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Parkinson's Disease, Alzheimer's Disease, and the Aging Brain

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From The Mount Sinai Medical Center, New York

Cedars-Sinai Medical Center

Mount Sinai Hospital
Medical Center of Chicago

Mount Sinai
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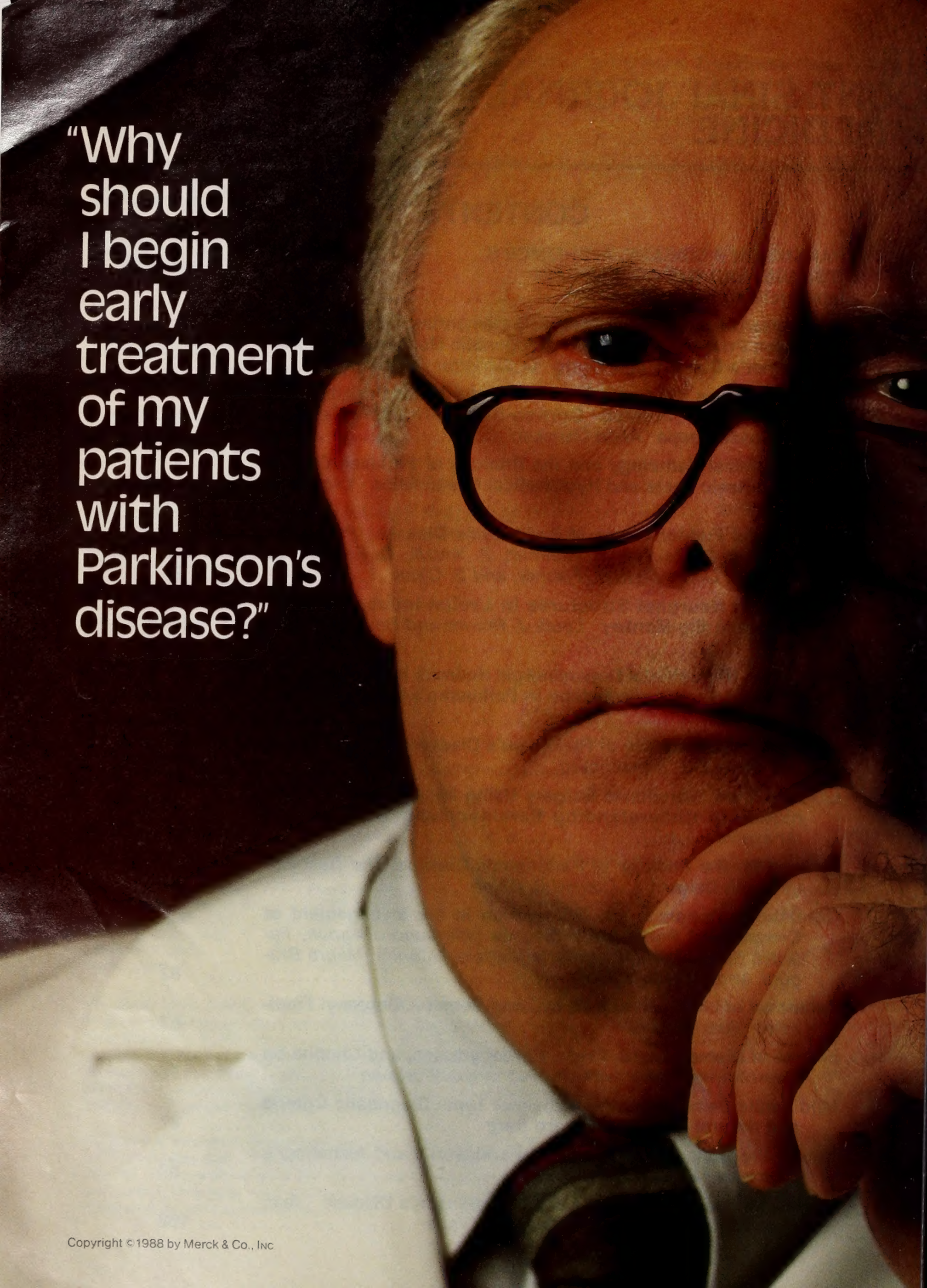
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[1] Markham, C. H. and Diamond, S. G.: Long-term follow-up of early dopa treatment in Parkinson's disease. Ann. Neurol. *19(4)*:365-372, April 1986.

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DISCONTINUE LEVODOPA AT LEAST 8 HOURS BEFORE STARTING SINEMET. The starting dose for SINEMET should provide about 25 percent of previous levodopa requirements. (Patients receiving less than 1500 mg of levodopa a day should be started on one tablet of SINEMET 25-100 t.i.d. or q.i.d.)

For full details on dosage and administration, see Prescribing Information.

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the Warnings (below) and Dosage and Administration sections in the Prescribing Information before initiating therapy.

Contraindications: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or history of melanoma.

Warnings: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See Dosage and Administration section of Prescribing Information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with* SINEMET *than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper GI hemorrhage in patients with history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatinine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

Precautions: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (ALT), SGPT (AST), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen, and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET® (Carbidopa-Levodopa, MSD) may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET.

Symptomatic postural hypotension can occur when SINEMET is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see Contraindications (above).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

Adverse Reactions: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, GI bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia, and agranulocytosis have occurred.

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (ALT), SGPT (AST), lactic dehydrogenase, bilirubin, blood urea nitrogen, protein-bound iodine, and Coombs test.

Other adverse reactions that have been reported with levodopa are: *Nervous System:* ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome. *Psychiatric:* confusion, sleepiness, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria. *Gastrointestinal:* dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhea, flatulence, burning sensation of tongue. *Metabolic:* weight gain or loss, edema. *Integumentary:* flushing, increased sweating, dark sweat, skin rash, loss of hair. *Genitourinary:* urinary retention, urinary incontinence, dark urine, priapism. *Special Senses:* diplopia, blurred vision, dilated pupils, oculogyric crises. *Miscellaneous:* weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

Overdosage: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

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For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486

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Introduction

Teresita S. Elizan, MD
Professor of Neurology
Mount Sinai School of Medicine
New York

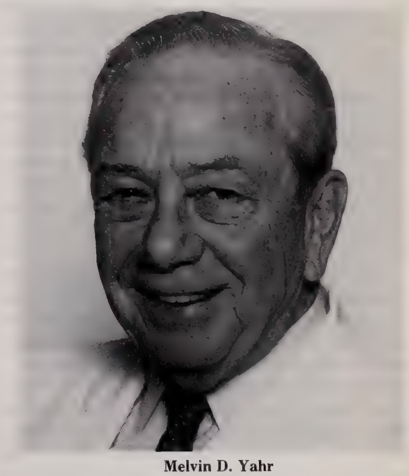
Parkinson's Disease, Alzheimer's Disease, and the Aging Brain

This issue of *The Mount Sinai Journal of Medicine,* devoted to recent research in two important neurological diseases, Parkinson's and Alzheimer's, is a celebration of the career and contributions of Professor Melvin D. Yahr, chairman of the Department of Neurology of the Mount Sinai School of Medicine (CUNY), on the occasion of his 70th birthday. An international group of investigators who have themselves contributed seminal work in their specific areas of research, and who over the years have had personal and professional ties with Dr. Yahr, join here to honor him.

Yahr's major contribution has been in the field of Parkinson's disease. In 1963, he organized at Columbia the Clinical Center for Research in Parkinson's Disease and Related Disorders, the first such multidisciplinary center, composed of basic scientists and clinical investigators working in various neuroscience disciplines. He later brought the center with him to the Mount Sinai School of Medicine when he took the chair of neurology in 1973. Under his superb guidance and intellectual leadership, the center, now the oldest in the country, and primarily supported by the National Institutes of Health, has made significant contributions in all the major aspects, basic and clinical, of Parkinson's disease and related movement disorders. Yahr has personally explored every relevant aspect of these disorders, from his pioneering role in the development of L-dopa therapy in Parkinson's disease and his conceptual formulations regarding the etiology and pathogenetic mechanisms of nigrostriatal dopamine deficiency, to his foresight on the importance of experimental brain transplant and of monoamine oxidase inhibitors in Parkinson's disease. He has written well over 200 papers on many of the major neurological problems of our time.

In addition to his research interests, he also happens to be one of the few truly great clinical neurologists today. A superb teacher, he has trained over a hundred neurologists in the last 14 years at Sinai, and has supported and stimulated many neuroscience investigators, here and abroad.

Research in Parkinson's and Alzheimer's Diseases. Parkinson's disease and Alzheimer's disease, two of the most common degenerative diseases of the aging brain, have generated considerable research interest in recent years. Two biological concepts in neurology that evolved in the 1960s provided the initial impetus for much of the current research in both diseases.



Melvin D. Yahr

The first concept, that a specific neurotransmitter deficiency is associated with a specific neurologic syndrome potentially amenable to replacement therapy, had its origins in Carlsson's pioneering suggestion in 1959 (1) that dopamine may be a transmitter in the central nervous system involved in the control of motor movements and in the parkinsonian syndrome, and in the now-classic 1960 paper by Ehringer and Hornykiewicz (2) which definitively showed a striking reduction of dopamine concentration in the neostriatum of cases of Parkinson's disease. These two papers led directly to the investigation of the effect of levodopa in Parkinson's disease and to the most effective medical replacement therapy for the disease to date (3–6). This dopaminergic system failure involving the nigrostriatal pathways in Parkinson's disease remains the significant starting point of most subsequent studies on etiology, pathogenesis, and treatment of the idiopathic form of the disease.

It was not until 1976–1977 that another neurotransmitter-specific system failure was initially reported for a second neurological disease, Alzheimer's, by three separate groups of investigators from the United Kingdom (7–9). The cholinergic marker enzyme, choline acetyltransferase, was found to be considerably reduced in Alzheimer's disease. This reduction, maximal in the temporal lobe, correlated with both degree of histopathologic change and clinical severity of dementia (10). The cortical cholinergic deficit in the Alzheimer's dementias remains the dominant, though not the exclusive, neurochemical substrate of the illness.

The second concept that determined certain lines of research on the fundamental cause of Parkinson's and Alzheimer's disease stemmed from Gajdusek's Nobel prize-winning discovery of a transmissible agent in kuru (11) and Creutzfeldt-Jakob disease (12)—the latter a primary dementing illness, as is Alzheimer's disease. It became possible to conceive that other progressive subacute and chronic neurologic illness, previously regarded as basically degenerative and noninflammatory, could be potentially infectious in etiology, and possibly virally induced, and that a prolonged latent interval, measured in years, between initial experience with a virus and such neurologic disorders may not be particularly unusual. Idiopathic Parkinson's disease was an obvious likely candidate as "slow viral infection," as was the parkinsonism-dementia complex of Guam (13, 14) and the Alzheimer's presenile/senile dementias. An intensive search for evidence of a viral presence or a specific immune response in Parkinson's disease has been essentially negative (15). Likewise, there has been no convincing evidence to date for an etiologic role of transmissible or nontransmissible, unconventional or conventional viruses in Alzheimer dementias (16–19).

The nature of the primary biochemical and structural insult in both Parkinson's and Alzheimer's disease remains the primary question. The basic neuronal degeneration at the core of these two diseases may be the result of a genetically programmed cell death, an age-related immune system dysfunction, a missing "trophic" substance or neuronal growth factor, an exogenous or endogenous toxin, an as-yet-unidentified virus or replicating agent—or a combination of any of these. The overlapping features of the two diseases at several levels (20) may, in fact, imply a common pathogenetic mechanism (21), which may eventually point to the fundamental cause.

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Transmissible and Nontransmissible Dementias: Distinction between Primary Cause and Pathogenetic Mechanisms in Alzheimer's Disease and Aging

D. CARLETON GAJDUSEK, M.D.

It is important to return our thoughts to the dichotomy always emphasized in medicine of a half century ago: that between cause, or etiology, and pathogenetic mechanism. In these days of molecular biology we are apt to confuse these two often very different problems. Elucidation of pathogenetic mechanism need not lead to discovery of cause, nor does discovery of cause lead to understanding of pathogenetic mechanism. Thus, the cause of the scrotal cancer of chimney sweeps and of the lip cancer of painters of the luminous dials on clocks and watches were discovered and the cancers eliminated long before mechanism was understood. Similarly, discovery of histamine release and its effects on cells and of the antihypersensitivity action of corticosteroids, the definition of their receptors, and the mechanisms of their action fails to lead to the discovery of the shrimp in the food, the bee sting, or the mites in housedust which gives rise to the acute angioneurotic edema, urticaria, ecchymoses, subcutaneous nodules, erythematous skin rash, chronic eczema or exfoliative dermatitis, acute or chronic asthma, chronic arthropathy, or other syndrome in a hypersensitive patient. The elimination of such hypersensitivity reactions or their prevention by avoidance of, or even desensitization to, the allergen have not required the reductionist analysis of mechanism. Understanding of the mechanism of the allergy was not required to effect cure or prevention; nor have the discovery and use of antihistamines, beta-blocking agents, or corticosteroids as pharmacologic agents required the understanding of their mechanism of action.

Thus, in dealing with chronic degenerative diseases of the central nervous system, as with hypersensitivities and neoplasms, we must not fool ourselves into believing that full elucidation of pathogenetic mechanism will lead us directly to cause or vice versa. Dementia paralytica, tabes dorsalis, gumma of the liver, and aortic aneurysm are all tertiary complications of infection with *Treponema pallidum* which we knew how to prevent and to treat, without having any idea of what determines which tertiary complication of syphilis any untreated subject will develop, or whether he will develop any complications at all.

Thus, we have fully realized that in isolating, sequencing, and further characterizing and chromosomally localizing the cDNA coding for the amyloid polypeptide of Alzheimer's disease and Down's syndrome and the aging brain we are not really pursuing "cause," but rather, mechanism. The cause of the premature appearance of neurofibrillary tangles in isolated populations in Guam, the Kii Peninsula of Japan, and in West New Guinea is an environmental variable which leads to neurofibrillary tangle formation in most individuals before middle age, and is followed by a very high incidence of amyotrophic lateral sclerosis and/or parkinsonism-dementia with cascading loss of specific sets of neurons. We believe that this is the result of deposits of cal-

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cium, aluminum, and silicon in neurons at an early age, secondary to adaptation to a very low level of environmental calcium and magnesium. The removal of the deficiency has led to the seeming disappearance of the early acquisition of neurofibrillary tangles in the populations and of amyotrophic lateral sclerosis and parkinsonism-dementia in all three foci.

Aluminum in dialysis dementia may be the "cause" of similar amyloid depositions, whereas it is central nervous system trauma that is the "cause" in pugilistic encephalopathy. In familial Alzheimer's disease a single autosomal dominant gene on chromosome 21 effects directly or indirectly the processing of the precursor protein to cause the formation of the 42-amino-acid polypeptide. This polypeptide assumes a beta-pleated sheet configuration and polymerizes into insoluble amyloid fibrils of neurofibrillary tangles and amyloid plaque cores. In Down's syndrome a duplication of the normal gene on the long arm of chromosome 21 (region q21–q22.1) along with the similar duplication of superoxide dismutase gene and the proto-oncogene ets-2 leads to both intracellular neurofibrillary tangles and extracellular amyloid plaques. Amyloid fibril deposition as neurofibrillary tangles and amyloid plaques or congophilic angiopathy occurs in all patients with Down's syndrome by 40 years of age. The "cause" in this case is surely the exogenous or endogenous factor responsible for prezygotic duplication of this region of the chromosome, which produces Down's syndrome in the developing fetus.

We now recognize two types of central nervous system amyloidosis: the transmissible type, of scrapie, Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, and kuru; and the nontransmissible type, of Alzheimer's disease, Down's syndrome, normal aging, pugilistic encephalopathy, and amyotrophic lateral sclerosis/parkinsonism-dementia in high-incidence foci.

The Transmissible Type of CNS Amyloidosis: A New Class of Microorganisms. In the first type of amyloidosis, precursor protein for the amyloid deposited in amyloid plaques and scrapie fibrils is specified by a normal gene of chromosome 20 in humans, and chromosome 2 in mice.

In this type the virus itself appears to be a subunit of these scrapie-associated amyloid fibrils, namely an amyloid beta-polypeptide in beta-pleated sheet configuration. Thus we have a nucleating process leading to initiation and autocatalytic acceleration, or enhancement, of amyloid fibril formation from the normal amyloid precursor protein. The "cause" is surely the unconventional virus of scrapie, kuru, or Creutzfeldt-Jakob disease. Its "infectivity" is inseparable from the glycosylated polypeptide (PrP33–35) polymerized to form subunits of the fibrils of scrapie-associated fibrils and the amyloid fibrils in the plaques of kuru, Creutzfeld-Jakob disease, and scrapie. Here, in these transmissible amyloidoses, we have thus discovered a new class of microorganisms which demand broadening our understanding of the basic tenets of biology—replication, cloning, mutation—which are really degradation, nucleation, autocatalytic augmentation, and crystallographic or configurational patterning events.

I would prefer to call the infectious agent of scrapie a *virus,* even if it proves to be as romantically exotic as a polypeptide directing an autocatalytically patterned degradation of a stagnated, pooled host-specified protein to a glycosylated amyloid. The potent abstract concept of a virus as a self-specifying transmissible entity requiring the machinery of the host for its replication did not demand any specific structure. Mathematicians playing with computers have not hesitated to use the term "virus infections" for threats to computer memories they have produced. Dewdney, with his Core Wars program, initiated computer virology. The fact that these mathematicians' software viruses contain no nucleic acid, and that nucleic acids are not in any way involved in the pathology that these viral diseases produce, has not prevented computer scientists from appropriately calling them viruses.

The Nontransmissible Type of CNS Amyloidosis. In the second group of brain amyloidoses (Alzheimer's disease, Down's syndrome, amyloidosis of the aging brain), we do not have transmissibility, but we have degradation and nucleation by calcium-silicon-aluminum deposits (as montmorillonites) which may cause a proteolytic cleavage and lead to autocatalytic enhancement of beta-pleated configuration by the beta-pleated polymerized polypeptide itself. In this case we are close to the fibril amyloid enhancement factors of Njiewold, Hol, van Andel, Lutz, and Gruys. I would conjecture at this point that our scrapie, kuru, Creutzfeldt-Jakob disease unconventional viruses may be completely analogous to these amyloid-enhancing factors, which now appear to be autocatalytic nucleating aggregates of the amyloid fibrils themselves.

If in Alzheimer's disease, Down's syndrome, and aging, nucleation events are required to initiate amyloid formation and precipitation, and thereafter aggregates of the 42-amino-acid betapolypeptide themselves accelerate and enhance the process, there will be a very fine line of distinction between our unconventional viruses causing transmissible amyloidoses and the nontransmissible amyloidoses which require some other "causative" nucleation, or starting or initiating event.

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Speculations on the Control of Mental and Motor Functions by Dopamine-Modulated Cortico-Striato-Thalamo-Cortical Feedback Loops

ARVID CARLSSON

Abstract

The hypothesis is advanced that the cerebral cortex is capable of protecting itself from an overload of information and from hyperarousal by means of negative feedback loops engaging the dorsal and ventral striatal complexes as well as the thalamus and the mesencephalic reticular formation. The thalamus can thus be looked upon as a filter for afferents from the outer world to the cerebral cortex. The feedback systems controlling this filter are modulated by the dopaminergic mesencephalo-striatal pathways. I suggest that the control system encompasses sensory, associative, and motor cortical functions.

Despite the enormous recent technical advances in brain research, we still do not know much about the mechanisms underlying higher mental functions. The discovery of the modern psychotropic drugs has opened up new avenues for research addressing this question, but a lot remains to be learned about the mode of action of these agents. The profound effects of some psychotropic agents on motor functions have also provided a platform for fruitful research on the regulation of movements, but again our knowledge of the mechanisms involved is far from complete.

Perhaps the most attractive starting point for a pharmacological approach to this problem is offered by the antipsychotic drugs. There is ample evidence that these agents are capable of alleviating dramatically the various aspects of the complex symptomatology observed in, for example, schizophrenic psychosis, at least in favorable cases. In normal individuals these drugs also cause profound mental changes, such as loss of interest, initiative, and creativity. It is now well established that the antipsychotic agents act by interfering with dopamine functions, and that the most important class of these drugs do so by blocking dopamine receptors in the brain. In fact, it is becoming increasingly clear that blockade of only one of the two subtypes of dopamine receptors, that is the dopamine D-2 receptor, is sufficient for an antipsychotic action. Whether selective blockade of D-1 receptors will also induce an antipsychotic action is not yet known (1).

The precise site of action of agents with such a profound effect on the mind is of course a matter of considerable interest. It is obviously not enough to be able to tell that we are dealing with an antidopaminergic action. We also have to answer the question where in the brain this action is located, and how effects on so many aspects of mental function can be brought about by interference with a single biological mechanism.

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Cortical versus Subcortical Mechanisms. Many workers in this field are inclined to believe that the antipsychotic action is located in the cerebral cortex. This is understandable in view of the ability of these agents to alleviate the profound schizophrenic thought disorders. However, in the present author's view there are strong arguments against this notion. Both the dopamine (2; G. Reynolds, personal communication; and unpublished data of the present laboratory, indicating dopamine levels generally below 10 ng/g in the human cortex) and the D-2 receptor levels (3) are extremely low in the human cerebral cortex. Admittedly, the brain, viewed as a cell society, is far from a democracy, and thus even a small number of nerve cells could occupy a strategic functional position. There is, however, one more argument to consider: It appears that in the evolution from lower primates to humans leading to the tremendous growth of the cerebral cortex, the cortical dopamine systems have not kept pace with the other cortical structures (cf. the monkey data of Brown et al., in ref. 4, with the human data quoted above). This suggests that the functions of cortical dopaminergic systems have largely been taken over by other mechanisms.

On the other hand, the subcortical dopaminergic systems, especially the striatal systems, are strongly developed in the higher primates, including humans. On the whole, the striatum, and along with it the striatal dopaminergic system (5), appear to have evolved in parallel with the cerebral cortex throughout the vertebrate subphylum (5). This, in conjunction with the intimate cortico-striatal connections (see below) makes the striatum a strong candidate in the search for the site of action of the antipsychotic drugs on the human mind. Needless to say, the cortical dopaminergic systems may still play a contributory role.

How could a subcortical structure have such a profound effect on cortical functions, such as the thought process? Recently, considerable progress has been made in the mapping of nervous pathways in the brain, including the connections between the cerebral cortex and subcortical structures (5–7). Based on the knowledge thus acquired, I present a hypothesis that tries to explain the role of the striatum and its dopaminergic systems for cortical functions.

Striatal Connections. According to a recently proposed system of nomenclature the striatum consists of two major parts: the dorsal and the ventral (6). The dorsal striatum, or neostriatum, consists essentially of the caudate nucleus and the putamen. Included in the dorsal striatal complex is the dorsal pallidum (globus pallidus). The ventral striatum consists of nucleus accumbens and several other dopamine-rich structures with intimate connections with the limbic system. These structures have often been referred to as the limbic dopaminergic structures. It is now evident that the ventral striatum is organized in a manner similar to the dorsal striatum. For example, the ventral striatum largely projects to a structure now known as the ventral pallidum. The dorsal and the ventral striatum differ in their connections, the ventral striatum being largely limited to the limbic system.

The striatum is connected to the cerebral cortex via a corticostriatal pathway. The dorsal striatum receives its cortical input mainly from the neocortex, and the ventral striatum is supplied from the (limbic) allocortex, although there is some overlap. It should be noted that the striatum receives fibers from all parts of the cortex, with a precise, though complex, topography (7). The traditional notion that the dorsal striatum, or neostriatum, serves an exclusively motor function is thus probably not correct. For example, the association areas of the frontal lobe project heavily onto the dorsal striatum. To emphasize the functional heterogeneity of this structure, Selemon and Goldman-Rakic (8) have introduced the term "association neostriatum," which includes the caudate nucleus and the anterior putamen, to be distinguished from the "motor neostriatum," which includes more posterior regions of the putamen.

From an evolutionary point of view, it seems reasonable to assume that motor and cognitive skills have evolved in close conjunction, and thus it is not surprising that the same is true of the corresponding anatomical substrates, that is, the cortex and the neostriatum. After erect walking had evolved in prehuman primates, the evolution of motor skill of the upper extremities was critical for the use and further development of mechanical tools. Along with this, evolution of intelligence was of course equally essential. The evolution of language and speech was equally based on advances in motor and cognitive functions.

A major projection of the striatum is on the thalamus. This is true of both the dorsal and the ventral striatum, whose main projections occur via the dorsal and ventral pallidum, respectively, to different thalamic nuclei. The thalamus is of course traditionally recognized as a relay station for afferent pathways projecting to the cerebral cortex. Thus an anatomic substrate for a cortico-striato-thalamo-cortical feedback loop is obvious (Fig.). Part of this feedback appears to be very precisely targeted. However, the thalamus harbors part of the reticular formation. Moreover, the dorsal as well as the ventral striatum, besides projecting on the thalamus, also possess major projections on the mesencephalic reticular formation.

A Thalamic Filter? The cortico-striatal projections appear to be essentially glutamatergic and have an excitatory influence on the striatum (9). The projections from the dorsal and ventral striatal complexes to the thalamus, apparently often with collaterals projecting on the mesencephalic reticular formation (6), appear to be largely inhibitory and possibly GABAergic. It follows, then, that we are probably dealing with negative feedback loops. In this context the thalamus could be looked upon as a filter for sensory inputs. This filter is under the control of the cerebral cortex via cortico-striato-thalamic loops. In this way the cortex is able to protect itself from an overload of information arising from the outer world via the sensory pathways to the thalamus, as well as from hyperarousal via the afferent pathways to the reticular formation.

The cortico-striato-thalamic loops, and thus the thalamic filter, are further controlled by the dopaminergic pathways projecting to the striatum from the mesencephalon. Since these pathways appear to be inhibitory on the striatum (10), it follows that they counteract the inhibitory influence of the cortex on the thalamic filter as well as on the arousal mechanism of the reticular formation. An increased dopaminergic tone would thus increase the information load on the cerebral cortex and cause arousal. Since the ventral striatum is under similar influence, the emotional loading of the incoming information reaching the limbic system will also be influenced by an increased dopaminergic tone, leading to mood elevation. A decreased dopaminergic tone would have the opposite effect, narrowing the thalamic filter, thus reducing the input to the cortex, inhibiting the arousal mechanism of the reticular formation, and lowering the mood level via an effect on the ventral striatum.

A decreased tone in the glutamatergic cortico-striatal pathway would be expected to induce behavioral stimulation similar to that induced by increased release of dopamine in the striatum. Accordingly, lesions in the prefrontal cortex or in the pathways from this region to the striatum have been found to cause behavioral "disinhibition" in monkeys and rats (10).

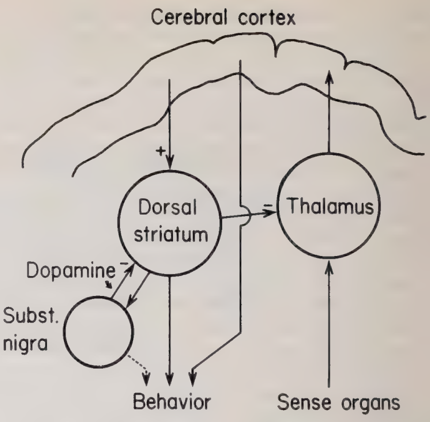

Fig. Schematic representation of hypothesis that cerebral cortex can protect itself from overload of information and from hyperarousal by means of feedback loops engaging striatal complexes and thalamus (as well as mesencephalic reticular formation, not indicated in figure). It is suggested that feedback loops are modulated by mesencephalo-striatal dopaminergic pathways.

The present hypothetical model, even if it should prove correct in essence, obviously involves considerable oversimplification. For example, the intrinsic circuitries of the various components of the model, that is the cortex, striatum, thalamus, and reticular formation, have been disregarded. If the approach proposed here turns out to be at all fruitful, these circuitries, needless to say, will have to be considered. A tentative sequence could be:

1. Cortico-striatal glutamatergic neurons (excitatory),
2. Intrinsic striatal cholinergic or GABAergic neurons (inhibitory),
3. Striato-pallidal GABAergic (inhibitory),
4. Pallido-thalamic GABAergic (inhibitory).

The mesencephalo-striatal dopaminergic neurons might preferentially function as inhibitors of the intrinsic striatal (no. 2 above) neurons. Moreover, other pathways, such as the ascending noradrenergic and serotonergic systems and the cholinergic system originating in the nucleus basalis Meynert, will have to be included. All these systems appear to have ample connections with the cortical and subcortical structures discussed above (6).

Neuropsychiatric Implications. Mania could be due to an increased dopaminergic tone, or to a lowered glutamatergic tone in the cortico-striatal pathway, leading to an opening of the thalamic filter and increased arousal. The opposite changes in these pathways could lead to depression. Schizophrenic psychosis might be due to an opening of the filter, leading to increased arousal. Whereas mania might result from an even opening of the filter, schizophrenic psychosis, with its bizarre apparent mixture of hyper- and hypo-arousal, might be due to regional differences in the filter function. For example, a defect in filter function, preferentially in the thalamic projections to the temporal lobe, might lead to auditory hallucinations. To counteract the defect, the negative cortico-striato-thalamic feedback loops, as well as the corresponding loops involving the reticular formation, might be activated, which could lead to hypoarousal in some regions and explain, for example, the so-called hypofrontality of schizophrenia.

Noteworthy is the apparent antagonism between the glutamatergic corticostriatal and the dopaminergic mesencephalo-striatal pathways. The well-known psychotomimetic action of phencyclidine (PCP) is of interest in this context. This agent seems to modulate glutamatergic, so-called NMDA receptors by combining with an allosteric site of these receptors (11). It would thus appear that a psychotomimetic action can be brought about either by reducing the glutamatergic or by raising the dopaminergic influence on the striatum, for example by amphetamine. This is in line with the model proposed here. A corollary would be that a glutamatergic agonist would have antipsychotic properties, provided that actions on other glutamatergic sites would not cause too serious side effects. No data to support or reject this hypothesis are available as yet.

The model proposed here would predict that not only mental but also motor functions would be under cortico-striato-thalamo-cortical feedback control and that this feedback loop, in turn, would be regulated by dopaminergic mesencephalo-striatal pathways. Indeed, animal experiments suggest a close connection between mental and motor functions following manipulation of dopaminergic mechanisms. For example, the well-established ability of antidopaminergic drugs to disrupt conditioned behavior has proved difficult to classify in terms of "mental" or "extrapyramidal" functions. Is, for instance, the lack of a conditioned response to a warning buzzer signal ("conditioned stimulus"), while the response to a mild painful stimulus ("unconditioned stimulus"), is still preserved following treatment with an antidopaminergic agent, related to a "sensory neglect," as observed after experimental destruction of dopaminergic pathways to the striatum (12), or does it rather correlate with the drug's extrapyramidal actions (13)? Also, human data point to a close connection between mental and motor functions. Thus, in Huntington's chorea, a disease caused by degeneration of striatal neurons, schizophrenic symptoms may precede the appearance of motor disturbances by several years (14). Conversely, untreated Parkinson patients characteristically show physical inertia, apathy, and lack of interest (15)—symptoms reminiscent of the action of antidopaminergic drugs on nonpsychotic individuals. Moreover, neurosurgery leading to alleviation of certain motor symptoms in Parkinson's disease involves destruction of tissue in the globus pallidus or the ventrolateral thalamic nucleus. This is in line with the present model, since the neurosurgical lesion would lead to a disruption of the cortico-striato-thalamo-cortical loop. Admittedly, not all Parkinsonian motor symptoms can be alleviated by neurosurgery, but perhaps a more detailed mapping of the pathways involved might improve the procedure. Of considerable interest in this context is the high incidence of mental side effects, including psychotic symptoms, following neurosurgery in Parkinson's disease. This is especially true following bilateral lesions or unilateral lesions in the dominant hemisphere (15).

These observations, taken together, strongly support the notion of a close anatomic relation between the striato-thalamic pathways engaged in the control of motor and mental functions. The question arises, to what extent could the motor deficits in Parkinson's disease be due to an abnormally strong inhibition at the thalamic level, because of loss of the inhibitory dopaminergic input to the striatum? In other words, could an extreme filtering off of incoming signals from the sensory pathways to the motor cortex lead to akinesia, rigidity, and tremors? In favor of this hypothesis is the remarkable ability of Parkinson patients to move in the face of acute danger—in the presence of fire, for example. In other words, if the sensory input is sufficiently strong to overcome the filtering mechanism, it may still induce significant motility. Similarly, choreatic symptoms might be due to an excessive input of signals from the periphery to the motor cortex, rather than to any direct disturbance in the motor system itself. Such symptoms could be due, for example, to destruction of cortico-striato-thalamo-cortical feedback loops, as in Huntington's chorea, or to excessive stimulation of dopaminergic receptors in the striatum, induced by an overdose of L-dopa.

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Neurochemical Pathology and the Etiology of Parkinson's Disease: Basic Facts and Hypothetical Possibilities

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Many chemical reactions and agents are known to be potentially damaging to nigral dopamine neurons. Among potentially damaging endogenous reactions are the excessive formation, through oxidative degradation of dopamine (either by autooxidation to melanin, or by deamination through the action of monoamine oxidase) of destructive oxygen radicals and hydrogen peroxide; the lack or the subnormal functioning of biochemical systems, including enzymes, for the detoxification of oxygen radicals, such as catalase, (unspecific) peroxidase, reduced glutathione, glutathione peroxidase and reductase, and superoxide dismutase. In addition to these endogenous factors, environmental toxins, including industrial poisons (herbicides and pesticides, carbon disulfite, manganese), as well as the meperidine analogue N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), have been shown to exert neurotoxic effects (1–3).

Since each of the suggested mechanisms, when activated in substantia nigra, may produce cell death of the nigral dopamine neurons, the conclusion has been drawn that some of them may actually be involved in the etiology of idiopathic Parkinson's disease. In addition to this neurotoxin hypothesis, the slow and progressive loss of nigral dopamine neurons with advancing age has also been postulated to be an important etiological factor, possibly superimposed on a single or long-term nigral insult produced by a neurotoxic agent (4).

All these hypothetical possibilities have one feature in common: they presuppose that the basic neurochemical alteration of the basal ganglia dopamine produced by the suggested cause is identical with, or at least qualitatively similar to, the dopamine changes in idiopathic Parkinson's disease. Therefore, in order to assess the validity of these hypotheses, knowledge of the basic neurochemical changes, especially in striatal dopamine, typical for idiopathic Parkinson's disease is absolutely necessary.

Basic Neurochemical Brain Changes in Parkinson's Disease

The discovery that Parkinson's disease is basically characterized by a profound loss of dopamine in the nuclei of the basal ganglia, especially substantia nigra, putamen, and caudate nucleus, has opened the way to a new understanding of this disorder as a disturbance of brain neurohumoral regulation; in addition, this discovery greatly stimulated research on brain neurotransmitters in general, both in health and disease. The most important practical-clinical result of this discovery was the introduction of the dopamine substitution concept, with L-dopa as the first rational and, as we now know, the most efficacious drug treatment of Parkinson's disease (5).

Although, in the course of time, changes in neurohumoral neurotransmitter-neuromodulator systems other than dopamine have been found in Parkinson's disease, it is the striatal dopamine deficiency that provided, and still provides, the basis for most of the progress in pathophysiologic, clinical, and pharmacotherapeutic research—including intrastriatal grafting of dopamine-producing tissue—into this disorder (6, 7).

The following short synopsis of the basic neurochemical brain changes in Parkinson's disease summarizes the most relevant data on the nigro-

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TABLE 1

Neurochemical Pathology of Parkinson's Disease: Changes in Brain Dopamine

Neurotransmitter marker (average change, % of control)*	Site of change
Nigrostriatal	
Dopamine (−70 to −90)	Caudate, putamen, s.nigra, pallidum
Homovanillic acid (−50 to −80)	Caudate, putamen, s.nigra, pallidum
Tyrosine hydroxylase (−75 to −85)	Caudate, putamen, s.nigra
Dopa decarboxylase (−85 to −95)	Caudate, putamen, s.nigra
Dopamine uptake (−60)	Putamen
D-2 dopamine receptor (+20 to +50)	Caudate, putamen
Dopamine stimulated adenylate cyclase (−70 to −80)	Putamen, caudate
Extrastriatal	
Dopamine, homovanillic acid (−60)	Accumbens; other subcortical limbic regions
Dopamine, homovanillic acid (−40 to −90)	Limbic cortex, neocortex

* − decrease; + increase.

striatal dopamine neurons; the limbic and cortical dopamine systems; and the nondopamine brain neurotransmitter-neuromodulator systems.

Nigrostriatal Dopamine Loss. The loss of dopamine in all components of the basal ganglia is the most consistent and the most specific neurochemical alteration in the brain of patients with Parkinson's disease. The corresponding changes (Table 1) include (a) severe loss of dopamine and its metabolites homovanillic acid, 3,4-dihydroxyphenylacetic acid, and 3-methoxytyramine in caudate nucleus, putamen (both called the striatum), globus pallidus, and the compact zone of the substantia nigra; (b) reduced concentration of the dopamine-synthesizing enzymes tyrosine hydroxylase and dopa decarboxylase; and (c) reduced number of the specific presynaptic dopamine uptake (transporter) sites (8).

TABLE 2

Relationship between Loss of Striatal Dopamine (DA) and Homovanillic Acid (HVA) and Severity of Parkinsonian Symptoms

Diagnostic grouping	Caudate		Putamen	
	DA %	HVA %	DA %	HVA %
PD (bilateral)*				
Mild akinesia	−78	−48	−87	−63
Marked akinesia	−92	−82	−98.5	−81
Hemiparkinson (right side)†				
Right striatum	−62	—	−80	—
Left striatum	−83	—	−96.5	—

* Data from Bernheimer et al., 1973 (10).

† Data from Barolin et al., 1964 (17).

The importance of the nigrostriatal dopamine loss for the pathophysiology of Parkinson's disease is well documented. Regardless of its etiology, Parkinson's disease is characterized by severe loss of dopamine in the basal ganglia, which has been found in idiopathic Parkinson's disease, postencephalitic parkinsonism, and senile-arteriosclerotic brain disease with parkinsonian symptomatology (9, 10). Marked striatal dopamine loss has also been found in degenerative brain disorders other than Parkinson's disease that involve parkinsonian symptoms, such as progressive supranuclear palsy (11), striatonigral degeneration (12), and neuronal intranuclear inclusion body disorder (13). Parkinsonism produced by neurotoxic compounds and certain psychotropic drugs is also characterized by loss of striatal dopamine. Examples include chronic manganese poisoning (10); the MPTP-induced condition in humans and in subhuman primates (14, 15); reserpine-induced reversible parkinsonism in humans (16). The reversible parkinsonian condition produced in patients by the dopamine-receptor-blocking neuroleptic drugs of the phenothiazine and butyrophenone series is due to a functional lack of dopamine at the postsynaptic, receptor level (16). In patients with Parkinson's disease, a significant correlation holds between the degree of striatal dopamine loss and the severity of nigral cell loss (10) (Fig. 1). The severity of the parkinsonian symptoms, for example akinesia, is positively correlated with the degree of striatal dopamine loss (10); this correlation also holds in persons with hemiparkinsonism, who sustain a more severe dopamine loss in the striatum contralateral to the affected side of the body (17–19) (Table 2). The ultimate confirmation and most crucial evidence for the pivotal role of striatal dopamine loss in the symptomatology of Parkinson's disease is the therapeutic success of dopamine substitution therapy, for example with L-dopa (5).

Together with the striatal dopamine deficiency as the most characteristic neurochemical alteration in the parkinsonian brain, the high antiparkinsonism efficacy of dopaminergic drugs provides a sound basis for the concept of dopamine substitution therapy as a rational approach to the pharmacology of Parkinson's disease. The potentiation of L-dopa's clinical effectiveness by means of inhibitors of the extracerebral dopa decarboxylase (carbidopa; benserazid) or monoamine oxidase (especially selective MAO-B inhibition with deprenyl) is based on, and further substantiates, the dopamine substitution concept. In addition, the fact that, in principle, dopamine substitution reverses all main motor symptoms of Parkinson's disease shows that dopamine is crucially involved in all major aspects of basal ganglia motor control.

Limbic and Cortical Dopamine Loss. A moderate to marked loss of dopamine, and of homovanillic acid, has been observed in many subcortical limbic regions of the forebrain (Table 1) (nucleus accumbens, medial olfactory area, lateral hypothalamus, the amygdaloid nucleus); in several limbic cortical and neocortical areas (parolfactory gyrus; entorhinal, cingulate, hippocampal, and frontal cortices); and in the area of origin of the dopamine projections to subcortical limbic and cortical regions, the mesencephalic ventral tegmental area of Tsai (20–24).

TABLE 3

Neurochemical Pathology of Parkinson's Disease: Changes in Nondopamine Neuron Systems

Neurotransmitter marker	Avg. change, % of control*	Site of change
Noradrenaline	−50	S.nigra, accumbens (straitum); many other regions
Serotonin	−50	S.nigra, striatum, accumbens; many other regions
Acetylcholine	+ (functional)	Striatum
Choline acetyltransferase	−30−−80	Cortex, (striatum)
γ-Aminobutyric acid	+70	Striatum
Glutamate decarboxylase	−50	Striatum, pallidum, s.nigra
Neurotensin	−70	S.nigra
Met-enkephalin	−65	S.nigra
Leu-enkephalin	−35	Putamen, pallidum
Cholecystokinin	−35	S.nigra
Substance P	−35	S.nigra, pallidum, putamen
Somatostatin	−45−−69	Cortex, hippocampus

* − decrease; + increase.

Changes in Nondopamine Neuron Systems. Significant changes in several nondopamine systems have also been observed in the parkinsonism brain (Table 3) (8). Reduced tissue concentrations in striatum, substantia nigra, globus pallidus, nucleus accumbens, limbic and/or cortical regions, hippocampus, cerebellar cortex, and spinal cord have been reported for noradrenalin; serotonin; the neuropeptides met- and leu-enkephalin, cholecystokinin, substance P, somatostatin, neurotensin; the gamma-aminobutyric acid marker enzyme glutamate decarboxylase; and the cholinergic neuron marker enzyme choline acetyltransferase. In contrast, the levels of gamma-aminobutyric acid in parkinsonism striatum have been found to be above normal; similarly, an increased cholinergic activity in the Parkinson striatum, due to loss of dopaminergic inhibition, can be deduced from observations in

TABLE 4

Actions of Non-DA Neurotransmitters on DA Activity in the Basal Ganglia and Their Possible Relation to Parkinson's Disease (PD) Symptoms

Neurotransmitter	Physiologic mode and site of action (interaction) with brain DA system	Change in PD	Probable effect on DA deficiency-related motor symptoms of PD
Noradrenaline*	Acts synergistically with mesotelencephalic DA system on motor activation	Decreased	Aggravation
Acetylcholine†	Produces catalepsy, enhances striatal DA deficiency symptoms (esp. rigidity, akinesia)	Functional + (due to DA loss)	Aggravation
Substance P‡	Stimulates DA neurons in s.nigra	Decreased	Aggravation
Cholecystokinin§	Facilitates certain DA neurons (esp. nucleus accumbens)	Decreased	Aggravation (?)
Serotonin‖	Inhibits DA neurons in s.nigra	Decreased	Amelioration
GABA#	Inhibits cholinergic activity in striatum	Increased (=deactivation?)	Aggravation (?) (via cholinergic activation)
Opioids/neurotensin**	Facilitate or inhibit DA neuron function, depending on site of action (cell bodies/terminals)	Decreased	?

* Svensson, 1971 (50); Andén et al., 1973 (51); Donaldson et al., 1978 (52); †Zetler, 1968 (53); Duvoisin, 1967 (54); ‡Glowinski et al., 1982 (55); Iversen, 1982 (56); §Crawley et al., 1985 (57); Vanderhaeghen and Crawley, 1985 (58); ‖Dray, 1981 (59); #Precht and Yoshida, 1971 (60); Gale and Casu, 1981 (61); **Havemann et al., 1980 (62); Nemeroff and Cain, 1985 (63).

TABLE 5

Biochemical Correlates of Compensatory Changes in Pre- and Postsynaptic Nigrostriatal Dopamine (DA) Neurons in Parkinson's Disease

	Caudate	Putamen
Presynaptic overactivity of remaining dopamine neurones leads to increase in molar ratio Homovanillic acid/Dopamine*		
Control	1.16	1.09
Parkinson	1.75	3.58
Postsynaptic denervation supersensitivity of striatal neurons to DA leads to increase in ^{3}H-haloperidol binding†		
Control	100%	100%
Parkinson	126%	155%

* Actual dopamine concentrations: control caudate, 2.46 μg/g; control putamen, 3.43 μg/g; Parkinson caudate, 0.36 μg/g; Parkinson putamen, 0.19 μg/g; from Bernheimer and Hornykiewicz, 1965 (64).

† Control caudate, 42 fmol/mg protein; control putamen, 44 fmol/mg protein; from Lee et al., 1978 (65).

experimental animals which show that normally dopaminergic neurons strongly inhibit the activity of the striatal acetylcholine neurons.

The role played by the dopamine changes outside the striatum and the changes in the nondopamine systems in the pathophysiology and clinical expression of Parkinson's disease is not definitely established. From experiments in laboratory animals it has been deduced that dopamine reduction in nucleus accumbens may aggravate the motor deficits of Parkinson's disease, whereas dopamine loss in other limbic or cortical regions may contribute to disorders of affect (depression) or cognition (dementia) sometimes seen in patients with Parkinson's disease. Regarding the nondopamine systems, complex interactions between most of them and the striatal dopamine neurons have been demonstrated. On the basis of these interactions, some changes (for example reduction in noradrenaline, substance P, cholecystokinin) may aggravate the parkinsonian symptomatology, whereas other changes (such as reduction in serotonin) may attenuate the striatal dopamine deficiency symptoms (Table 4). However, since most of these changes are small in comparison with the profound striatal dopamine loss, they may be fully compensated for by the remaining neurons, and thus not produce any overt functional, clinical deficits.

Striatal Dopamine Loss and Idiopathic Disease

In idiopathic Parkinson's disease, the striatal dopamine loss is neither diffuse nor uniform. Therefore, in addition to explaining nigral cell death and striatal dopamine loss, a valid hypothesis proposing neurotoxins, or aging, or both, as the cause or causes of idiopathic Parkinson's disease has to satisfy at least two neurochemical criteria: (a) the characteristic interregional pattern of striatal dopamine loss found in idiopathic Parkinson's disease; and (b) the subregionally uneven loss of dopamine within both the putamen and the caudate nucleus.

Specific Inter- and Sub-Regional Patterns of Loss. In respect to the interregional pattern of striatal dopamine loss, in idiopathic Parkinson's disease the putamen is regularly more severely affected than the caudate nucleus, losing over 95% of dopamine, compared with approximately 80% dopamine loss in the caudate nucleus (10) (Fig. 2). On the subregional level, there is also a clear difference between the putamen and the

TABLE 6

Striatal Dopamine in Parkinson Syndromes of Different Etiology and in Senescent Human Brain

Striatal subdivision	Dopamine in % of control			
	Idiopathic*†	Postencephalitic*	MPTP-induced (rhesus monkey)‡	Old age§‖
Interregional				
Caudate (whole)	−84 (2.64)	−98.5 (2.64)	−99.5 (8.81)	−64 (6.60)
Putamen (whole)	−98 (3.44)	−99.4 (3.44)	−99.4 (10.23)	−55 (8.76)
Subregional				
Caudate, rostral	−91 (2.91)	—	−99.7 (7.69)	—
caudal	−67 (3.83)	—	−99.3 (10.03)	—
Putamen, rostral	−96 (5.20)	—	−99.4 (11.41)	—
caudal	−99.5 (5.51)	—	−99.6 (9.15)	—

Percent values calculated from *Bernheimer et al., 1973 (10); †Kish et al., 1986 (25); ‡Pifl, Schingnitz, and Hornykiewicz, in preparation; §Kish, Shannak and Hornykiewicz, in preparation. (Values in parenthesis, actual dopamine levels, in μg/g, of corresponding controls.) ‖Mean age 80 years (controls: 30 years = 100%).

caudate nucleus. Thus, the caudal subdivisions of the putamen are much more severely affected by dopamine loss than the rostral putamen (25) (Fig. 3). Specifically, in many cases with idiopathic Parkinson's disease, the caudal putamen is nearly completely depleted of its dopamine (less than 1% dopamine remaining), whereas the rostral putamen may still contain between 4% and 12% (Kish, Shannak, and Hornykiewicz, in preparation). In contrast, in the caudate nucleus the most rostral part of the head is usually more severely affected (91% dopamine loss) than the caudal head, where up to 40% dopamine can still be found.

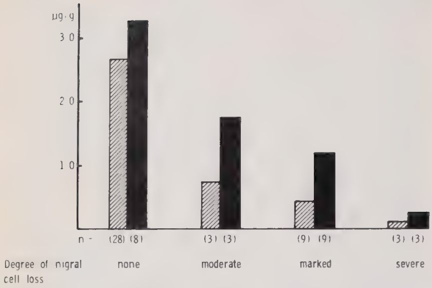
Morphologic Basis of Uneven Subregional Loss. The morphologic basis for the uneven pattern of striatal dopamine loss in idiopathic Parkinson's disease is to be found in the specific pattern of cell loss in the compact zone of the substantia nigra. This pattern of nigral cell loss characterizes the idiopathic disorder and distinguishes it from other varieties of parkinsonism. Thus, Hassler (26) has shown that in idiopathic Parkinson's disease (a) the caudal two-thirds of the substantia nigra zona compacta are much more severely affected than the rostral one-third of this nucleus; and (b) within the rostral substantia nigra, only the medial and ventral (central) cell subgroups show some cell loss; in contrast, in the caudal substantia nigra the cell loss is severe to practically complete throughout the ventral and ventrolateral subdivisions. Interestingly, the most medial portion of the caudal substantia nigra is regularly spared in idiopathic Parkinson's disease (26).

Patterns of Loss and Etiology. Apart from their importance as a distinguishing mark of idiopathic Parkinson's disease, the characteristic patterns of striatal dopamine loss represent a reliable criterion by which we can judge the validity of any etiologic hypotheses of this disorder. Because the striatum cannot function normally without a concurrent intact dopamine input from the substantia nigra (27), idiopathic Parkinson's disease as a clinical entity must be critically determined by the highly variable inter- and subregional loss of striatal dopamine. In this regard, the role played by the specific patterns of striatal dopamine loss cannot be fully appreciated without taking into account that (a) the nigrostriatal dopamine neurons possess a high compensatory capacity when faced with partial dopamine loss; and (b) the putamen and the caudate nucleus have basically different roles in basal ganglia function.

Role of Neuronal Compensatory Capacity. The manifestation of clinical symptoms of Parkinson's disease as a consequence of the striatal dopamine loss is a threshold phenomenon requiring a critical reduction in dopaminergic influence on the striatal function. This threshold for functional striatal decompensation is the direct result of the particularly high capacity of the remaining nigrostriatal dopamine neurons to compensate for smaller neuronal losses (8). The extent to which the brain dopamine system is capable of functionally compensating for the lost neuronal activity is clearly shown by the observation that Parkinson's disease symptoms do not become clinically manifest unless the striatum loses 80% or more of its dopamine (10) (Fig. 4). The molecular basis for this unusually high adaptive capacity includes overactivity of the remaining neurons as well as the development of denervation supersensitivity of the postsynaptic dopamine receptor sites in the striatum (28) (Table 5).

Since within the unevenly-dopamine-depleted striatum, functional decompensation will take place only in the most markedly affected subdivisions, it is easy to see that the final pattern of the functional deficits—the manifestation of clinical symptoms of Parkinson's disease—will be crucially determined by the adaptive capacity of the remaining neurons. By compensating for smaller dopamine losses, this adaptive capacity will impress not only the neurochemical pattern but also a functional pattern on the striatum. The clinical symptoms of Parkinson's disease can thus be regarded as the result of the characteristic pattern of the actual dopamine loss modified by the adaptive capacity of the remaining dopamine neurons.

Functional Heterogeneity of the Striatum. The characteristic interregional and subregional patterns of striatal dopamine loss in idiopathic Parkinson's disease are important because of the neuroanatomical heterogeneity and functional diversity of the striatal nuclei (29–31). In this respect, the putamen is part of a cortical-subcortical loop system with predominantly motor relationships, receiving most of its cortical input from the premotor and motor-sensory cortex; in contrast, the cortical input to the caudate nucleus comes from all parts of the frontal association cortex. These differences in connectivity have led to the notion that the function of the putamen is closely related to extrapyramidal motor control (such as planning and execution of learned motor programs), whereas the caudate nucleus may be



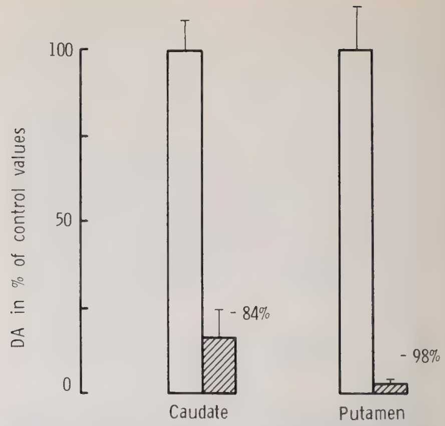


Fig. 1. **Left** Idiopathic Parkinson's disease: Correlation between degree of nigral cell loss (zona compacta) and levels of dopamine (cross-hatched columns) and homovanillic acid (black columns). Note shift of ratio of dopamine to homovanillic acid in favor of the latter. Data from Bernheimer et al., 1973 (10). **Fig. 2.** **Right** Different degree of dopamine loss in caudate nucleus and putamen in patients with idiopathic Parkinson's disease (cross-hatched columns). Data have been taken from Bernheimer et al., 1973 (10) and expressed in % of controls (white columns).

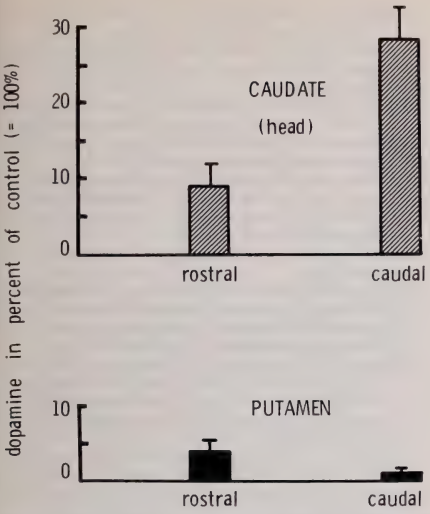
more intimately involved with complex psychomotor function, including the motivational aspects of motor behavior. Since the striatum cannot function normally without a normal dopaminergic innervation (27), the strikingly uneven loss of dopamine within the functionally heterogeneous striatal gray must by necessity result in highly characteristic and specific patterns of functional loss.

Taken together, these observations clearly bear out the crucial importance of the inter- and subregional patterns of striatal dopamine loss for the characterization of idiopathic Parkinson's disease as a clinical and neurochemical entity in its own right; moreover, they demonstrate that the characteristic patterns of loss can serve as reliable biochemical criteria in studies related to the etiology and pathogenesis of idiopathic Parkinson's disease, setting it apart from parkinsonian syndromes of other etiologies.

Idiopathic Parkinson's Disease: Result of Interaction between Aging and Environmental Insults to Substantia Nigra?

In the context of the hypotheses implicating, as possible etiological mechanisms/factors in idiopathic Parkinson's disease, nigral insults due to exogenous (environmental) or endogenous toxins alone or in conjunction with the normal loss of nigral dopamine neurons with advancing age, the specific patterns of nigral cell loss and striatal dopamine characteristic for idiopathic Parkinson's disease assume special importance. The crucial question then is: Does a nigral neurotoxin such as MPTP or normal aging of the nigrostriatal dopamine neurons produce interregional and subregional patterns of dopamine loss in striatum qualitatively similar to the patterns found in idiopathic Parkinson's disease? It is obvious that, if the neurotoxin/aging hypotheses are to be valid, at least one of the suggested etiological factors, a MPTP-like neurotoxin or aging, should in this respect mimic the characteristic striatal dopamine patterns found in idiopathic Parkinson's disease.

MPTP-Induced Parkinsonism in the Rhesus Monkey. No data on dopamine in striatum of humans with MPTP-induced parkinsonism have so far been obtained, but a number of studies have documented striatal dopamine changes in primates with MPTP-induced parkinsonism (32–44). In most of the MPTP-treated monkeys studied, the depletion of dopamine in caudate nucleus and putamen was profound, averaging 95% loss. In most instances, the differences between putamen and caudate were small, between 2% and 5%, and the caudate nucleus seemed to be more affected by dopamine loss than the putamen. In two studies, it was found that the dopamine depletion in substantia nigra had a definite pattern, the central substantia nigra being most severely depleted of dopamine, and the most



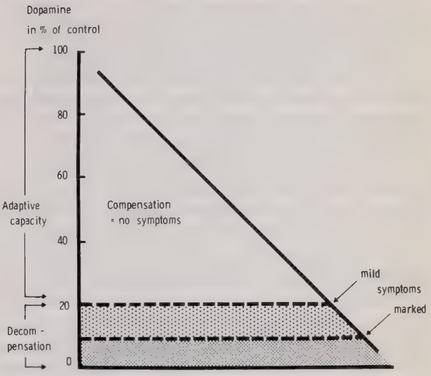


Fig. 3. **Left** Different subregional pattern of dopamine loss in caudate and putamen in patients with idiopathic Parkinson's disease. Data taken from Kish et al., 1986 (25). **Fig. 4.** **Right** Adaptive capacity of nigrostriatal dopamine neuron system and compensated and decompensated stages of Parkinson's disease. Note that symptoms become clinically manifest only when 80% or more striatal dopamine is lost—decompensated stage of Parkinson's disease. Diagram based on data obtained by Bernheimer et al., 1973 (10).

medial substantia nigra subdivision being relatively spared (35, 45). If confirmed in further studies, this would be an interesting observation because Hassler (26) has shown that in idiopathic human Parkinson's disease, there is no cell loss in the most medial part of substantia nigra. Despite this highly interesting similarity between idiopathic human Parkinson's disease and MPTP-parkinsonism in the monkey, the pattern of actual dopamine neuron loss in MPTP-treated monkeys does not resemble the patterns in idiopathic human Parkinson's disease (45): in the neurotoxin-produced condition there is, judged from literature, no interregional pattern favoring dopamine loss in putamen as is the case in idiopathic Parkinson's disease.

In one of my own studies (46) designed to explore further the interregional and subregional patterns of MPTP-induced striatal dopamine changes, permanent parkinsonian symptoms (bradykinesia and akinesia, flexed posture, postural tremor, freezing episodes) were induced in four rhesus monkeys by repeated intramuscular injections of small doses (0.15–0.4 mg/kg) of MPTP. After a survival period of 6 weeks to 7 months, the striatal dopamine concentrations in the MPTP-treated monkeys were severely reduced, being less than 1% of control levels. However, there were no apparent interregional or subregional differences typical for idiopathic Parkinson's disease (Table 6). Thus, the dopamine loss in the caudate nucleus (99.5%) was at least as severe as in the putamen (99.4%). This confirms the results published in the literature. In addition, rostral and caudal subdivisions of the putamen and caudate in the MPTP-treated monkeys seemed equally affected by dopamine loss, there being no indication of the distinct rostrocaudal pattern seen in idiopathic Parkinson's disease. In general, it can be said that in our MPTP-treated rhesus monkeys the loss of dopamine in the striatum mimicked more closely the picture typical of postencephalitic parkinsonism (10) than that of the idiopathic disease (Table 6). However, in our experiments the striatal dopamine loss produced by MPTP was practically maximal. Therefore, the effect on striatal dopamine pattern of MPTP doses below the threshold of clinically manifest Parkinson's disease should be studied.

Effect of Aging on Striatal Dopamine Pattern in Human Brain. There is sufficient evidence to show that humans undergo age-related decay of the nigrostriatal dopamine neuron system (46, 47); on average, approximately 6% of nigral dopamine neurons are lost per decade of life. At the age of 60 years, there is usually a 40%–50% reduction of striatal dopamine; although substantial, this loss by itself is not sufficient to produce overt symptoms of Parkinson's disease, because the remaining dopamine neurons compensate (47); symptoms do not become clinically manifest unless 80% striatal dopamine has been lost.

A comparison of the magnitude of dopamine loss in the caudate and putamen in a group of five senescent patients (mean age 80 years) versus a younger age group (mean age 30 years; n = 5) showed (Table 6) that the age-related dopamine loss in the caudate nucleus (64%) was slightly greater than the loss in the putamen (55%) (48). This in general confirms an earlier observation (49) and indicates that age-related striatal dopamine loss does not mimic the interregional caudate-putamen pattern of idiopathic Parkinson's disease, the changes in these two conditions being, as a matter of fact, in opposite directions. However, the subregional pattern of striatal dopamine loss during aging has yet to be studied in the human brain.

Conclusions. From our preliminary observations it can be concluded that neither the MPTP-induced dopamine changes nor the striatal dopamine loss due to physiologic aging seems to reproduce the typical pattern of dopamine loss in idiopathic Parkinson's disease. If this conclusion is correct, then the typical nigral cell loss, and consequently the pattern of striatal dopamine loss, in idiopathic Parkinson's disease is most likely produced by mechanisms or chemical factors basically different from the processes underlying normal aging of the nigrostriatal dopamine neurons and exogenous or endogenous neurotoxins with MPTP-like mechanism of action.

Although environmental factors such as MPTP (and many other neurotoxins), or an interaction between such factors and aging, may produce nigral cell loss and corresponding striatal dopamine loss sufficiently severe to result in parkinsonian symptoms, this clinical condition most probably may be best categorized as secondary parkinsonism. From our admittedly preliminary observations it would appear that the primary cause of the idiopathic variety of Parkinson's disease still remains unknown.

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Biochemical Fundamentals of Parkinson's Disease

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Biochemical studies are the basis for the assumption that the progression of Parkinson's disease (PD) is due to the continuous denervation of central dopaminergic systems predominantly affecting nigrostriatal fibers. Degeneration of noradrenergic systems arising from the locus ceruleus and lateral reticular formation, and of serotonergic fibers arising from cell bodies of the raphe is thought to depend on a differential loss of respective neurons. In addition, PD associated with dementia shows degeneration of the cholinergic nucleus basalis of Meynert, cortex projection (1–4). Although the biochemical changes in the late, decompensated stage of PD are well documented, not much evidence has been gathered on the early, compensated phase or the time course of this disease (3, 5, 6).

Presynaptic Changes

Bernheimer et al. (1) describe a high correlation of nerve cell loss in substantia nigra (SN) pars compacta and reduction of dopamine (DA) and homovanilic acid (HVA) in the striatum and, in particular, in the putamen. However, the cause of the continuous progress of this degeneration is not known. Benign and malignant types of PD have been described, indicating a possible but unknown difference in the time course of PD. Moreover, classification of PD into tremor-dominant (T) type, rigidity-akinesia (RA) type, or equivalence (RAT) type (7–9) seems to confirm differences in the underlying process and in the progress of denervation (intensity, localization). The late decompensated phase of PD is correlated with variable topography of morphologically visualizable lesions in the brain. In addition, multitransmitter disturbances of varying origin and intensity occur and are related to varying degrees of motor deficiency and loss of intellectual capacity (4, 10). It is not entirely clear whether those multitransmitter changes are already dominant in the initial and preclinical phase of the disease or at least at the start of the clinical phase when the triad of akinesia, rigidity, and tremor is apparent.

Biochemical studies support the view that the beginning of PD can be expected 15 to 20 years before clinical onset and diagnosis (11). In healthy controls the reduction of DA in the caudate nucleus is 12.8% ± 3.1% per decade, with a loss of 15.3% to 15.7% between age 45 and 66 years, and a reduction of 9.8% to 10.7% at more advanced ages. The loss of DA in the caudate nucleus of PD starting at age 60 ± 1 years was 28.6% ± 0.9% in the early compensated phase (67 to 73 years). Patients whose disease began when they were older (73 ± 1 years) showed comparable loss of DA in the early phase (28.3% ± 4.2% at age 74 to 80 years) as well as the late phase (38.6% ± 5.8% at age 80 to 84 years).

This finding of a pronounced loss of DA in PD in the early and especially in the late, decompensated phase shows the high capacity of nigrostriatal DA fibers to overcome the morphologic lesion by functional means, that is, increase of DA turnover (Table 1). It is assumed that the high plasticity of the brain in overcoming dener-

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TABLE 1a

Clinical Characteristics, Control and Benign Parkinson's Disease (PD) Subjects

	N	Age	Sex	Disease duration (yrs)	Post-mortem time, hrs (mean)	Rx	Dx	Neuropathology
Controls	4	77 (74–83)	1M/3F		7.5 (4–11)	antibiotics cardiovascular treatment	heart infarction (2) bronchopneumonia (2)	age-related brain histology
PD	5	79 (75–82)	2M/3F	10 (8–13)	6.5 (3–9)	combined L-dopa amantadine	Parkinson's disease (5)	Lewy bodies loss of melanin in SN

Data taken from Riederer et al. 1986 (43).

TABLE 1b

Dopamine, DOPAC, and HVA in the Caudal and Rostral Putamen of Benign Parkinson's Disease (n = 3–5)

Putamen site	Dopamine	DOPAC mean as % of 3–4 controls	HVA
Caudal	11	19	41
Rostral	39	79	72

TABLE 2b

Dopamine, DOPAC, and HVA in Malignant Parkinson's Disease (PD)

	Dopamine	DOPAC % of controls	HVA
Putamen	4	10	29
S. nigra	7	2	48
Hippocampus	47	68	106
Fr. Cortex	66	38	66

Data are means of 3 to 6 brain areas in Parkinson's disease and of 3 to 4 regions in controls; dopamine was measured with a coulometric HPLC-ECD method; metabolites were determined with HPLC-ECD (Sofic 1986, 44).

TABLE 2a

Clinical Characteristics, Control and Malignant Parkinson's Disease (PD) Subjects

	n	Age (yrs)	Sex	Disease duration (yrs)	Post-mortem time (h)	Rx	Neuro-pathology	Dx
Controls	4	71 (69–76)	2 M/2 F		6.0 (3–9)	antibiotics, cardiovascular Rx	age-related normal	edema of lung heart failure angina pectoris myocardial lesion
Parkinson's disease	6	74 (70–79)	2 M/4 F	4.5 (3–6)	5.5 (3–8)	combined L-dopa amantadine until 2 days before death	Lewy bodies degeneration of s. nigra, loss of melanin	PD (5); PD plus akinetic crisis (1)

Data taken from Riederer et al. 1986 (43).

vation processes ensures functional accuracy up to a loss of around 70%, whereas a higher degree of degeneration can be compensated for only by supplementation of DA. Data of Hornykiewicz and Kish (12) and of Riederer et al. (43, Table 1) favor the assumption that less denervated subareas of the striatum show a smaller reduction of DA and HVA than more severely degenerated areas. It can be expected that malignant PD (Table 2) is at least in part due to pronounced loss of cells in the SN pars compacta. Although the pathobiochemical basis of PD is not known, the concentration of DA may well be lower in patients with malignant PD before the start of the disease, which is triggered by events as yet unknown. The functional activity of monoaminergic neurons is known to be age-dependent, because of the nonlinear decrease in the rate-limiting enzyme tyrosine hydroxylase (TH) in the striatum (13) and the continuous nonlinear decrease in DA (11, 14). The age-dependent increase in monoamine oxidase (MAO) type B, which deaminates amines such as phenylethylamine and dopamine, but not of MAO type A (serotonin and noradrenaline as substrates) contributes additionally to changes in the neuronal function of DA systems, that is, age-dependent changes in nigrostriatal plasticity.

Presynaptic compensation is expressed roughly by the ratio of DA and HVA. This ratio is 0.25 in younger PD patients (mean age 66 years) and 0.32 in older patients (mean age 83 years) (15). HVA, the main metabolite of DA, is primarily synthesized extraneuronally. The concentration of this metabolite reflects the amount of released DA. In contrast, 3,4-dihydroxyphenylacetic acid (DOPAC) is thought to be synthesized mainly intraneuronally. The concentration of this metabolite is low compared to HVA. At a low degree of degeneration the reduction of DOPAC is similar to that of HVA, but at a higher degree of denervation the reduction is more pronounced (Table 1). The change in DA:DOPAC ratio seems to better reflect denervation of the presynaptic neurons, whereas the DA:HVA ratio seems to be a better indicator of compensatory capacity and of DA function of postsynaptic receptors. Both loss of vesicular storage capacity for DA and loss of cytosolic TH activity are an expression of the degree of denervation and can be correlated with the actual decrease in DA.

The role of TH in the pathogenesis of PD is only poorly understood; for example, we do not know whether the loss of TH activity is due to co-factor changes, altered phosphorylation properties, or simply incomplete synthesis. Rausch et al. (16) recently reported on TH activity of human postmortem brain tissues from controls and patients with PD, examined in the presence of Fe^{++} and phosphorylation agents such as cAMP, exogenous protein kinase, calcium plus calmodulin (Ca^{++}-CaM), and ATP. TH activity in parkinsonian tissue was 48% higher than in controls in the presence of exogenous protein kinase (Table 3), a statistically significant increase. cAMP alone had no effect, whereas Ca^{++}-CaM increased TH activity by only 10% (16). The presence of acetylcholine resulted in a slight decrease in enzyme activity. Human TH was stimulated 13.17-fold in the presence of 1mM Fe^{++}. For iron dependence no significant differences could be shown for the Km values of TH in striata of PD; the activity of TH was 60% of that of controls (Table 4). Here stimulation with 1mM Fe^{++} raised the activity of TH 11-fold.

The specific topography of denervation in any one patient is vital to our understanding of the pathophysiology of PD and the consequences of pharmacologic therapy, including possible adverse reactions. We assume that when L-dopa is administered to a given patient, it reaches that patient's innervated, partly denervated, and completely denervated neuronal structures that have different compensatory capacities. Thus a particular patient may respond to the drug with improved akinesia, but also has other, adverse reactions (hyperkinesia, dystonia) that limit the benefit of the drug. The variability of drug response may depend on different affinities for DA in innervated or denervated receptors.

Postsynaptic Changes

According to Kebabian and Calne (17), two types of postsynaptic receptors exist. The D1 receptor is adenylate-cyclase-dependent, the D2 receptor is independent of this enzyme. In PD, reduced, normal, and increased receptor densities have been noted (3). There is general agreement that striatal D2 receptors do not degenerate in PD and that their function, even in the late, decompensated phase, is ensured. In PD these receptors respond to dopaminomimetics with downregulation, whereas in neuroleptics receptor density increases (3). Because receptor density and affinity are merely biochemical criteria for demonstrating the quality of ligand binding to the receptor protein(s), no interpretation or correlation with physiologic and behavioral output—motor response—can be made.

Our own studies show no change in receptor number and affinity in about one-third of PD patients who died during an akinetic crisis and were drug resistant in the late stage of the disease (Table 5).

A more recent work by Guttman et al. (18) shows no change in D1 receptors in PD, and a mild increase in the number of D2 receptors in drug-free patients. In drug-treated patients with PD, near normal values were obtained. Although these findings challenge the concept of denervation supersensitivity, it may be that more pronounced differences, i.e. increase in receptor number in drug-naive patients, can be measured in subareas of the striatum with lesions >90%. Neuropathologic findings show that this high degree of neuronal loss is indeed not obligatory in the SN (1, 4) but may occur topically.

Pathophysiologic Aspects and Parkinson's Disease

The basal ganglia are ideal sites for the degenerative action of free radicals (19, 20) because they are high in lipid and oxygen consumption and have elevated concentrations of metals (iron and copper) and increased metabolic activity resulting in hydrogen peroxide formation. Thus the basal ganglia are highly susceptible to the cellular degenerative actions of lipid peroxidation (21). It is excess hydrogen peroxide in contact with reduced transition metals (Fe^{++} and Cu^{+}) that liberates free radicals, such as the highly

TABLE 3

Stimulation of TH in Human Caudate Nucleus under Phosphorylating Conditions
(nmoles DOPA formed/g tissue per hr ± SEM)

Group (no. brain areas)	−PK	+PK	% of basal value	significance
Controls (13)	40.3 ± 4.1	48.2 ± 6.0	118 ± 26	NS
Parkinson (14)	18.6 ± 3.7*	24.9 ± 3.7*	148 ± 14	$p < 0.05$

Homogenates from human brain caudate nucleus were incubated together with or without the stimulating agent as specified under methods.

NS, not significant; PK, protein kinase (3 μg).

* $p < 0.05$ compared to corresponding control levels.

Data taken from Rausch et al. 1987 (16).

TABLE 4

Stimulation of TH in Postmortem Human Caudate Nucleus by Ferrous Ion
(nmoles DOPA formed/g tissue per hr ± SEM

Group (no. brain areas)	TH activity		(% of control value)
	Basal	Stimulated	
Controls (9)	8.3 ± 2.4	109.3 ± 22.3*	(1317)
Parkinson (11)	5.0 ± 1.4	54.7 ± 13.8*+	(1100)

Homogenates from human brain caudate nucleus were incubated in the standard assay system in the presence or absence of 1 mM Fe^{++}.

* $p < 0.01$, compared to basal levels.

+ $p < 0.05$ compared to controls.

Data taken from Rausch et al. 1987 (16).

TABLE 5

^{3}H-Spiroperidol Binding in Postmortem Putamen of Parkinson's Disease (PD)
(mean ± SEM)

PD* treated with L-dopa + DI amantadine sulfate† (no. pts)	B_{Max} (pmol/g)	K_D (nM)
Responder (15)	19.3 ± 1.42	0.18 ± 0.03
Nonresponder (5)	19.8 ± 1.55	0.20 ± 0.021
Controls (25)	20.6 ± 1.87	0.14 ± 0.027

B_{Max} and K_D values were determined from Scatchard analysis; receptor binding technique, according to Seeman 1980 (45).

* Histologically verified by K. Jellinger 1986 (4); all groups were matched for age (range 69–80 years), sex, and postmortem time (<10 hours). Duration of PD in responder group, 11.5 ± 2.3 years; it was shorter in nonresponders (8.7 ± 2.1 years).

† Long-term treatment with L-dopa plus benserazide 62.5–187.5 mg/day; amantadine sulfate 300–400 mg/day for responder and nonresponder.

reactive cytotoxic hydroxyl radical (·OH), which in turn induces lipid peroxidation processes. Catalase, the enzyme most effectively responsible for the decomposition of hydrogen peroxide and the prevention of cellular damage (22), is virtually absent in the brain. However, glutathione peroxidase, which also decomposes hydrogen peroxide, is present, but its activity is largely dependent on the availability of reduced glutathione (23). Therefore it may be expected that under conditions in which excessive amounts of hydrogen peroxide are available, as a result of either overproduction or decreased breakdown, the basal ganglia will be rendered susceptible to damage by free radicals formed from it. Monoamine oxidase, whose reaction involves the formation of hydrogen peroxide (24), has been suspected of participating in this phenomenon (25, 26), since the basal ganglia have the highest activity of the enzyme (27). Furthermore, evidence has been presented that monoamine oxidase B activity increases in the brain with advancing age (28).

Other factors that may also contribute to the degenerative process in PD are the increased availability of free or protein-bound iron (ferritin) and a reduction in the high concentration of the powerful antioxidant ascorbic acid in the brain (19, 29, 30). Ascorbate, however, is thought to have dual effects: not only does it promote radical reaction; it is also able to react quickly with O_2^- and ·OH radicals. Hence it acts as a prooxidant at low concentrations and as an antioxidant at high concentrations (21).

Furthermore, dopaminergic cell bodies of the substantia nigra seem to be extremely susceptible to radical processes, as indicated by a high dopamine turnover, dopamine autooxidation processes leading to neuromelanin, and the high affinity of neurotoxic substances, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

We therefore measured the amount of several metals, ferritin, glutathione, and ascorbic acid in brains and transferrin in ventricular cerebrospinal fluid in postmortem materials from parkinsonian subjects and compared them to those in matched control brains. We were also interested in studying the influence of hydrogen peroxide on TH and MAO activity.

Since iron is transported to the brain by a special protein, transferrin, we measured various iron-dependent proteins, total iron, iron-related blood components, and hematocrit in the plasma of parkinsonian patients. There were no significant differences in these measurements (Table 6), but there were differences in the concentration of transferrin in postmortem ventricular cerebrospinal fluid (Table 7). These data indicate a

TABLE 6

Iron-Related Routine Determinations in Serum of Long-Term Hospitalized Parkinsonian (PD) Patients

Group	No. pts.	Total iron (μg/dl)	Transferrin (mg/dl)	Ferritin (μg/l)	Hemoglobin (g/dl)	Hematocrit (%)	Erythrocytes Mio	Reticulocytes ‰
Control (range, routine clinical chemistry assays)		60–150	20–400	10–200	12–18	36–48	4.1–6.0	7–15
PD (mean ± SEM)	24	79 ± 5.7	220 ± 9.8	295 ± 42.6	13.8 ± 0.26	42.2 ± 0.7	4.52 ± 0.1	10.7 ± 1.2

All PD pts were women, mean age 77.3 years (range 68–85 years); mean duration of PD, 10.3 years (range 2–23 yrs). PD pts were on usual antiparkinsonism treatment (L-dopa + peripheral decarboxylase inhibitor benserazide, n = 20, 2–3 × 62.5 mg/day up to 2–3 × 125 mg/day; amantadine sulfate, n = 17, 1–3 × 1/day; terguride, n = 13, 2 × ½–3 × 2/day. Antidepressants, n = 9, neuroleptics, n = 9; lisuride, n = 2; anticholinergics, n = 4. Additional diagnoses were depression, n = 4; diabetes, n = 3; cardiac failure, n = 3; SDAT, n = 4; MID, n = 7; hemiparkinsonism, n = 3. Only 5 pts had concentration of total iron lower than 60 μg/dL; 10 pts had higher concentrations (>200 μg/L) of ferritin. Ceruloplasmin, which oxidizes ferrous to ferric iron, was not changed in this series of experiments.

change in the mechanism of iron transport across the blood-brain barrier or the blood-cerebrospinal fluid barrier in brains of PD patients.

We compared the regional distribution of copper, zinc, magnesium, and calcium in parkinsonian brains with the distribution in matched controls. Although no significant difference between the two groups in the amount of these elements was found, marked regional distribution of iron, magnesium, and calcium was present (31). The most notable was the concentration of iron, which was highest in globus pallidus and was also concentrated (in descending order) in putamen, substantia nigra, caudate nucleus, red nucleus, dentate nucleus, amygdaloid nucleus, raphe nuclei, plus reticular formation.

A markedly lower glutathione content was present in putamen, globus pallidus, substantia nigra, nucleus basalis of Meynert, amygdaloid nucleus, and frontal cortex of mild parkinsonism. In these areas ascorbic acid was also decreased (31). Glutathione and ascorbic acid are well recognized for their ability to prevent free radical formation from interaction of iron with hydrogen peroxide. The reduction of these two radical scavengers in regions of the parkinsonian brain, having high iron concentrations together with an increase of ferritin in substantia nigra (Table 8), suggests a possible link between the generation of free radicals and a facilitation of radical-induced denervation by an increased release of iron from ferritin. There is, however, no conclusive evidence to support this assumption. For example, the free iron concentration is not changed in the caudate nucleus of PD (Table 9).

Effect of Hydrogen Peroxide and Iron Salts

TH activity. Hydrogen peroxide decreases TH activity only at high concentrations (16). Species differences are noted for the combined incubation of Fe^{++} and H_2O_2. In the gerbil caudate nucleus,

TABLE 7

Transferrin in Postmortem Ventricular CSF

	No. samples	Transferrin mg/l (means ± SEM)
Controls	3	19.0 ± 1.0
Parkinson's disease	4	11.3 ± 1.1*
Huntington's chorea	3	15.1 ± 1.0**
Liver cirrhosis	3	26.2 ± 3.8

All samples were matched for sex, age (range 51–88 yrs), and postmortem time (range 3–16 hrs). *$p < 0.004$; **$p < 0.005$ vs. controls.

TABLE 8

Ferritin in Human Brain of Controls and Parkinson's Disease (PD) Subjects (mean ± SEM, μg/g fresh tissue)

	Ferritin		
	Controls* (no. tests)	PD† (no. tests)	p
S. nigra	223 ± 21.5 (5)	288 ± 27.3 (5)	<0.05
Putamen	240 ± 31.3 (5)	328 ± 52.0 (5)	<0.09

For determination, a dissociation-enhanced lanthanide solid phase two-site fluoroimmunoassay based on the direct sandwich technique with polyclonal antibodies was used (DELFIA Kit 1244-008). Groups were matched for sex (3 females, 2 males), age (range 72–78 yrs), and postmortem tissue (range 6–14 hrs).

* Died from cardiovascular failure and bronchopneumonia; this group did not receive drug treatment influencing central nervous system.

† Treated with combined L-dopa treatment (Madopar 62.5 to 125 t.i.d.) until three days before death. No other antiparkinsonism treatment was given.

TABLE 9

Iron Content and pH in Human Caudate Nucleus of Controls and Parkinson's Disease (PD) Subjects

Group (no. brain areas)*	pH	Free iron (n moles/g)	Total iron (μmol/g dry wt)
Controls (7)	5.68 ± 0.3	355 ± 53	388 ± 93
PD (7)	5.50 ± 0.4	328 ± 31	404 ± 63

* Groups matched for sex, age (range 70–78 yrs), and postmortem time (3–13 hrs).

TABLE 10

Influence of Hydrogen Peroxide and Iron Salts on Activity of Monoamine Oxidase in Brain (% of controls ± SD)

Sample	Cortex parietalis			Putamen		
	PEA	5-HT	DA	PEA	5-HT	DA
H_2O_2 10^{-3} M	335 ± 67	82 ± 4	105 ± 19	210 ± 17	81 ± 4	102 ± 12
$FeCl_2$ 10^{-3} M	37 ± 11	52 ± 16	42 ± 8	44 ± 13	61 ± 17	38 ± 8
$FeCl_2$ 10^{-3} M & H_2O_2 10^{-3} M	290 ± 54	68 ± 12	54 ± 18	209 ± 6	65 ± 16	30 ± 8
$FeCl_3$ 10^{-3} M	104 ± 6	89 ± 2	58 ± 17	101 ± 4	87 ± 4	60 ± 6
$FeCl_3$ 10^{-3} M & H_2O_2 10^{-3} M	342 ± 93	74 ± 8	50 ± 4	216 ± 18	73 ± 8	42 ± 3
$MgCl_2$ 10^{-3} M	102 ± 6	98 ± 2	93 ± 8	101 ± 3	99 ± 4	97 ± 2
$MgCl_2$ 10^{-3} M & H_2O_2 10^{-3} M	352 ± 101	86 ± 6	109 ± 15	217 ± 17	85 ± 4	109 ± 14
100 % value nmol × min^{-1} × mg $protein^{-1}$	0.5 ± 0.1	1.2 ± 0.2	1.0 ± 0.3	1.2 ± 0.3	1.4 ± 0.1	2.0 ± 0.5

n = 3, each determination in duplicate. MAO substrates used: phenylethylamine (PEA): 20 μmol, serotonin (5-HT): 200 μmol, dopamine (DA): 200 μmol. Time of preincubation: 1′ with H_2O_2. Incubation period: 30′ with 5-HT or DA, 10′ with PEA.

H_2O_2 does not prevent the stimulating properties of Fe^{++}; the pig shows a dose-related decline in TH activity. No data are available on this effect in humans. We have in progress an analysis of this important issue, using postmortem brains of PD patients and controls.

MAO activity. MAO measured in postmortem human putamen and parietal cortex shows that H_2O_2 significantly increases MAO-B activity when phenylethylamine (PEA) is the substrate but not when 5-HT or DA are used as substrates. Ferric chloride does not change MAO activity when PEA or 5-HT is the substrate, but activity does decrease with DA as substrate. Ferrous chloride decreases MAO activity (PEA, 5-HT, DA as substrates). MAO-A activity (5-HT as substrate) showed a smaller decline compared to PEA or DA (Table 10). Combined incubation of H_2O_2 and ferric chloride or ferrous chloride did not change the stimulation of MAO-B that is noted with H_2O_2 alone.

The specificity of effects observed with iron salts was confirmed by incubation of MAO with magnesium chloride. This salt did not cause any change in MAO activity compared to controls, and it had no influence on H_2O_2-induced MAO-B activity (Table 10).

These experiments indicate that iron salts do not potentiate the H_2O_2-induced stimulation of MAO-B activity.

Conclusions

Metals, especially Fe^{++}, have always been suspected of having a role in cytotoxicity and cell degeneration. For this reason, the importance of metals in promoting the formation of highly reactive radicals (O_2^-, ·OH) from hydrogen peroxide suggested that a study of their metabolism in the parkinsonian brain could be of importance in understanding the underlying cause of this nigrostriatal dopaminergic degenerative disease (19, 32, 33). The results of the present report and of an earlier study (31) clearly show no profound differences in the amounts of these elements in control and parkinsonian brains except for ferric iron in SN (31). However, this finding is at variance with recent findings by Dexter et al. (34), who reported increased iron and copper in globus pallidus and substantia nigra of parkinsonian brains. These data contrast with earlier reports (35) that iron was consistently increased by a factor of two or more above the control values in caudate nucleus and globus pallidus.

This topic disturbance of iron metabolism does not negate the highly cytotoxic role of this metal if present in free form. A near-normal concentration of free iron (Table 9) does not exclude the possibility of a relative increase in degenerated neurons. However, not only low-molecular-weight iron complexes but also some iron proteins, such as ferritin, known to be present in the brain (36) can rapidly catalyze hydrogen peroxide decomposition into the highly reactive hydroxyl radicals (·OH) and O_2^- which, in turn, promote the chain reaction of lipid peroxidation. This process, if allowed to continue long enough, causes the gradual loss of membrane fluidity and loss of membrane integrity (21).

Although the increase of ferritin noted in the substantia nigra and putamen of Parkinson's disease subjects is moderate, it may be sufficient to be involved in cytotoxic action. In this regard the decreased amounts of glutathione and ascorbic acid in various brain areas (31) are of special significance. Earlier reports indicated that brain peroxidase and catalase activities were lowered in Parkinson's disease (37). Lowered glutathione (38, 39) and glutathione peroxidase (40) led Perry et al. (38) to suggest that PD may be a disorder resulting from nigral glutathione deficiency.

Glutathione and ascorbic acid are utilized as scavengers of free radicals formed by the interaction of iron and hydrogen peroxide and have a major role in cellular detoxication (25). However, our studies (Table 10) are not in line with the assumption that iron salts potentiate effects of H_2O_2 on both TH and MAO enzyme activity. This, however, does not exclude any potentiation of lipid peroxidation by iron salts leading to membrane decomposition (21). Even though iron is thought to be intimately involved with dopamine receptor synthesis and dopaminergic neurotransmission (41), there is no evidence to confirm these experimental studies in PD (18). If iron and radicals derived from H_2O_2 play a role in the pathogenesis of PD, their deleterious effects primarily affect the dopaminergic cell bodies in SN as well as the nerve terminals in the striatum.

Although the free-radical hypothesis is attractive, the present state of knowledge does not allow any definite conclusion on the role of iron and free radicals in the pathogenesis of PD. In particular, the beneficial effects of a therapeutic complex composed of sodium-ferrico-ferroso 2,3-diketogulonic acid and sodium-ferrico-alloxanic acid in PD (42) are evidence of a bimodal action of iron.

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Brain Stem Neuronal Structures in Lesion-Induced Parkinsonism in the Monkey

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Introduction

In a previous study involving the brain of the monkey, cat, and rat and, to a lesser extent, the human brain (1), we described different types of neurons composing the substantia nigra (SN) and topographically related groups of neurons or nuclei at upper brain stem level. More specifically we studied the cytological characteristics and the numbers and sizes of the various types of neurons as well as their particular distribution. Four main types of neurons were identified in the SN of these species. They include the compacta, reticulata, intermediary, and globular types of neurons. The primate SN, however, contains relatively fewer neurons of the globular type. In other and earlier studies we established good correlations between the importance of retrograde cell degeneration at the level of the SN and other related nuclear groups and the decreased concentrations of monoamines (dopamine, serotonin, noradrenalin) at the level of the neostriatum (caudate nucleus and putamen) following lesions, mostly unilateral, involving the rostral midbrain ventromedial tegmentum in monkeys and cats (2–4). We also established good correlations between such morphological changes and/or the associated neurochemical striatal disturbances and the production of resting tremor, rigidity associated with the cog-wheel phenomenon, and akinesia following midbrain tegmental lesions in the monkey (3–7).

Taking account of these findings, we now wish to more precisely define the retrograde neuronal degeneration (cell loss) associated with a unilateral lesion restricted to the ventral tegmental area of Tsaï (VTA type lesion) or involving a larger area of the midbrain ventromedial tegmentum including the VTA (VMT type lesion). The present report also aims at establishing a closer relationship between the morphologic changes and the associated decreased concentration of striatal monoamines and the production of parkinsonlike motor disturbances in the monkey. The brains of several monkeys (*Macaca mulatta*) with different upper brain stem lesions collected over the last twenty years were available for this study.

Results

Retrograde cell degeneration or cell loss associated with unilateral midbrain lesions of either the ventromedial tegmentum (VMT) or the ventral tegmental area (VTA) involves different groups of neurons that appear to be mostly, if not exclusively, located on the side of the lesion at

TABLE 1

Mean Number of Neurons of the Three Main Types in the Substantia Nigra of Monkeys with Unilateral Lesions involving the Corresponding Nigrostriatal Pathway

	Compacta	Reticulata	Intermediary
Lesioned side	2 100 (1322)*	8 587 (2396)	2 060 (370)
No. of animals	8	8	4
Unlesioned side	62 624 (5433)	8 772 (2589)	2 112 (754)
No. of animals	8	8	8
% les./unles.	3.0	98	98

* Standard deviation.

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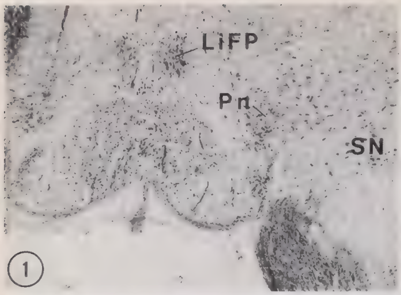
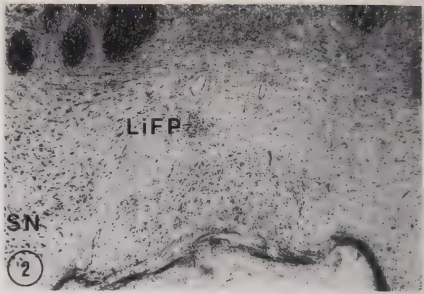
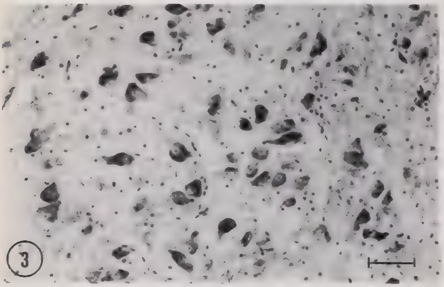
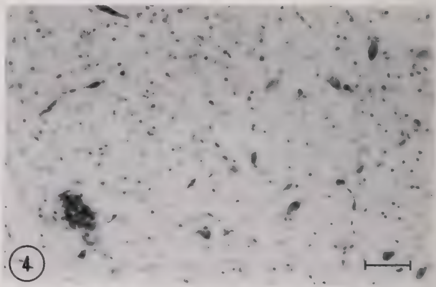




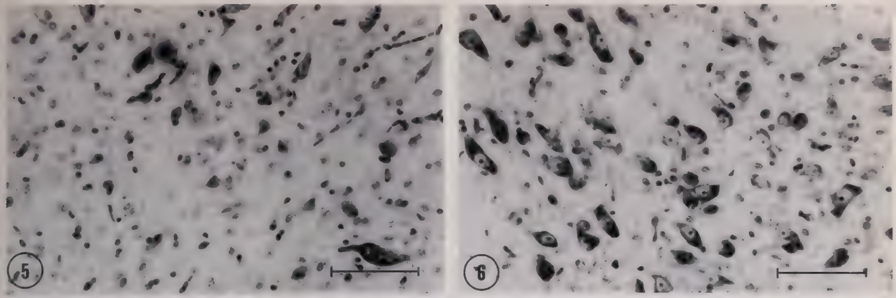


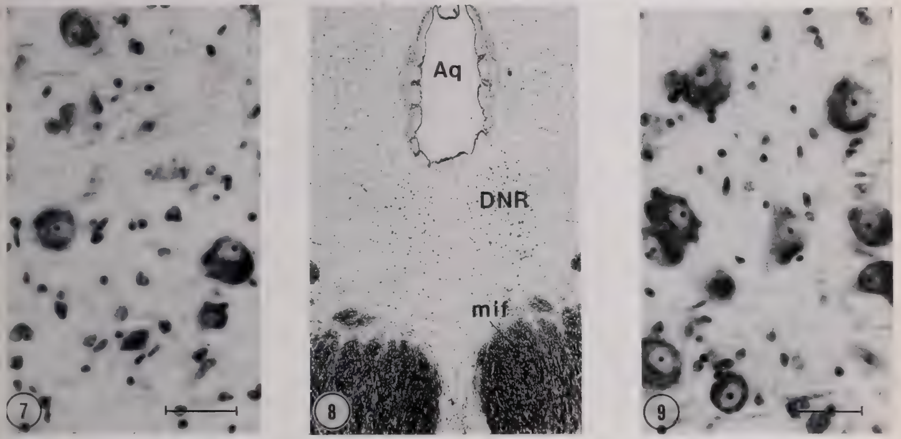


Figs. 1,2. Photomicrographs of transverse sections through caudal part of base of midbrain in normal monkey (**Fig. 1**) and in another monkey (**Fig. 2**) with unilateral lesion at level of rostral part of ventromedial tegmentum (VMT). Note cell loss in the "foyer pédiculaire" of linear nucleus (LiFP), paranigral nucleus (Pn), and substantia nigra (SN) on lesioned (right) side. Luxol fast blue and cresyl violet. Original magnifications, ×40. **Figs. 3,4.** Photomicrographs through pars compacta of substantia nigra of monkey with unilateral ventromedial tegmental lesion (VMT) interrupting corresponding nigrostriatal pathway. Note marked cell loss (**Fig. 4**) in compacta of lesioned side. Same stain. Scale bars, 100 um.

the level of the midbrain and upper pons. This does not exclude the possibility that certain groups of neurons may undergo degeneration following bilateral interruption of the corresponding efferent neurites, or else, certain groups of neurons may not show any conspicuous morphologic changes following complete interruption of their efferent fibers. The latter feature is well illustrated by the neurons of the locus coeruleus, which appear normal after extensive lesions interrupting their ascending fibers which, however, are associated with a sustained and important decrease of noradrenalin in the cerebral cortex of the lesioned side in cats and rats (8, 9).

VTA Type Lesions. Unilateral lesions involving the rostral part of the ventral tegmental area (VTA type lesions) are associated with a severe cell loss of the compacta type neurons in the pars compacta and pars dorsalis (or nucleus parabrachialis pigmentosus) of the substantia nigra (SN) on the corresponding side (Table 1, Figs. 3, 4). Such lesions also result in a marked cell loss in the ipsilaterally located ventrolateral and dorsomedial paranigral nuclei and in the so-called "foyer pédiculaire" of the central linear nucleus (Figs. 1, 2, 5, 6). The dorsalmost and caudalmost part of the dorsal nucleus of the raphé (DNR) corresponding to the paramedian nucleus of Ziehen also displays an important cell loss on the side of the VTA lesion. At the level of the SN, the cell loss is very severe and specifically involves the compacta type neurons (Figs. 3, 4) which, as previously reported (1), are more especially located within the pars compacta and pars dorsalis of the SN. The other types of neurons of the SN, and more especially the reticulata and intermediary types, do not present any sign of retrograde degeneration and their numbers are within normal range on both sides of the brain (Table 1). The cell rarefaction or loss observed at the level of the other structures of the midbrain and pons includes almost all neurons (most of which are of the compactalike type) of the ventrolateral division of the paranigral nucleus and the larger neurons of the dorsomedial division of the same nucleus, as well as some of the larger neurons of the





Figs. 5,6. Photomicrographs through paranigral nuclei of monkey with unilateral lesion of ventral tegmental area (VTA) at level of rostralmost part of midbrain. Note marked cell loss on side of lesion (**Fig. 5**) in comparison to unlesioned side (**Fig. 6**). Same stain. Scale bars, 100 μm. **Figs. 7,8,9.** Photomicrographs illustrating dorsal nucleus of raphé (DNR) of both sides in monkey with unilateral ventromedial tegmental (VMT) lesion. Incomplete but important cell loss on side of lesion may be observed on left side of **Fig.** 8 immediately above medial longitudinal fasciculus (mlf); in higher magnification in **Fig. 7. Fig. 9** illustrates corresponding neurons on the unlesioned side. Same stain. Original magnification, ×25, **Fig.** 8; Scale bars, 50 μm, **Figs. 7 and 9.**

so-called "foyer pédiculaire" of the central linear nucleus (Figs. 1, 2, 5, 6) recently described by Poirier et al. (1). A few compactalike neurons irregularly interspersed between the latter structures in the caudal and ventromedial part of the midbrain also undergo degeneration.

Therefore almost all larger neurons located in the retrorubral cupuliform area undergo a severe degeneration following rostrally located VTA lesions. This area, which has been named by Foix and Nicolesco (10), encompasses many of the cell groups that are described here as undergoing degeneration: the medial part of the pars compacta and the pars dorsalis of the SN, both divisions of the paranigral nucleus, the so-called "foyer pédiculaire" of the central linear nucleus, and other compactalike neurons diffusely dispersed within and between these structures. In fact, most of the neurons still present in this area on the lesioned side are pale and small (diameter less than 10μm). The cell loss observed in the caudal part of the DNR or nucleus of Ziehen following a VTA lesion is at the expense of the larger neurons of this paraventricular division of the DNR. Such unilateral VTA lesions are associated with a marked decrease of dopamine (DA) in the ipsilateral striatum but, under such conditions, the concentration of the striatal serotonin (5-HT) appears within normal range (Table 2).

Finally monkeys with unilateral lesions restricted to VTA do not present any detectable motor impairment, in spite of the fact that such

TABLE 2

Mean Concentrations (μg/g) of Dopamine (DA), Serotonin (5-HT), and Noradrenaline (NA) in Striata of Monkeys with Unilateral Lesions involving Ventromedial Tegmentum (VMT) or Exclusively the Ventral Tegmental Area (VTA) of Midbrain*

	Lesioned side			Unlesioned side		
	DA	5 HT	NA	DA	5 HT	NA
VMT (7)†	.29	.07	.14	4.94	.26	.30
	.19‡	.06	.12	2.46	.18	.12
VTA (4)	.59	.47	—	3.65	.54	—
	.45	.13	—	.98	.17	—

* Based on results reported by Poirier, Sourkes et al., 1966.

† Number of animals.

‡ Standard deviation.

lesions cause a severe cell loss of neurons, including those of the SN compacta type, and result in associated decreased concentration of striatal DA.

VMT Type Lesions. Unilateral lesions which involve the rostral or preoculomotor part of the VTA (as described above) and the structures located immediately above—in other words, a lesion that extends between the VTA, ventrally, and the parvocellular division of the red nucleus and the oculomotor nucleus, dorsally—also result in a marked cell loss in various structures of the midbrain and upper pons on the ipsilateral side. Such lesions of the ventromedial tegmentum (VMT type lesions) are associated with cell losses at the level of the SN and the cupuliform area which are very similar to those resulting from a VTA lesion, as described above. As a matter of fact the pars compacta and pars dorsalis of the SN and the ventrolateral division of the paranigral nucleus display an almost complete or very severe cell loss and there is a conspicuous cell rarefaction in the other structures of the cupuliform formation and in the paramedian nucleus of Ziehen following VMT lesions (Table 1, Figs. 1–6).

VMT lesions do not cause any noticeable degeneration of the SN reticulata and intermediary types of neurons (Table 1). VMT lesions, however, are associated with retrograde cell degeneration in other groups of neurons located in the raphé of the upper pons and caudal midbrain. Thus, conspicuous cell losses, mostly at the expense of the larger neurons, are observed at the level of the "foyer linéaire" of the central linear nucleus, as supposedly described by Cajal (11), and in the subfascicular (12) and interfascicular divisions of the caudal linear complex as described by Castaldi (13) and Crosby and Woodburne (14). VMT lesions also cause a cell loss in the ventral (angustus of Ziehen), central, and lateral divisions of the DNR (Figs. 7–9). It is more important in the ventral (angustus) and lateral (wing) parts of the nucleus. The nucleus angustus corresponds to that part of the DNR that lies between both medial longitudinal fasciculi.

Similarly to VTA lesions, unilateral VMT lesions are associated with very important decreased concentrations of striatal DA. In addition they also result in an important decreased concentration of 5-HT and in a somewhat less significant decrease in NA concentration in the ipsilateral striatum (Table 2). Moreover, such VMT lesions may be associated with motor disturbances in the limbs contralaterally to the lesions. The main disturbances include a parkinsonlike tremor and hypokinesia or rigidity associated with the cogwheel phenomenon. VMT lesions involving more dorsally located structures in addition to those mentioned above, namely, in the vicinity of and below the periaqueductal gray, may also result in dystonia and circling movements.

VMT lesions, of course, also involve descending nervous pathways and other structures in addition to those related to the monoaminergic neurons and corresponding nervous pathways. In particular, VMT lesions interrupt more or less extensively ascending cerebellofugal fibers as well as nervous fibers descending homolaterally in the central tegmental tract and/or contralaterally in the rubro-tegmento-spinal tract. In addition, neurons of the parvocellular and/or magnocellular division of the red nucleus may be more or less extensively degenerated or destroyed.

Conclusions and Summary

The neuronal rarefaction or cell loss observed in SN pars compacta, paranigral groups of neurons, and rostrally located nuclei of the raphé following unilateral VTA or VMT lesions at rostral midbrain level appears to involve almost exclusively neurons located on the lesion side. As a matter of fact, cell counts involving the various types of neurons on both sides of the SN not only in monkeys, as shown in this study (Table 1), but also in cats and rats with VTA or VMT lesions (unpublished data) suggest that a majority of the corresponding ascending fibers travel ipsilaterally at least as far as the hypothalamus. They most likely correspond to the ascending dopaminergic (DA) fibers.

Other groups of neurons closely associated with the compacta-type neurons on the basis of their cytological characteristics, such as those of the "foyer pédiculaire" of the central linear nucleus and paranigral nuclei (1), also project predominantly, if not exclusively, to the homolateral side of the diencephalon and telencephalon. The corresponding groups of fibers most likely represent DA and, to a lesser extent, 5-HT fibers.

In addition, other nuclear groups of the raphé ("foyer linéaire" of the central linear nucleus, subfascicular and interfascicular divisions of the caudal linear complex, the dorsal nucleus of the raphé, including its most caudal neurons represented by the paramedian dorsal nucleus of Ziehen) also undergo a partial retrograde degeneration ipsilaterally to the side of the VMT type lesion in the monkey. A majority of the neurons which undergo degeneration under such conditions are most likely also monoaminergic (especially DA and 5-HT) neurons, on the basis of studies involving histofluorometric approaches in this species (15–17). These features (18, 19) pointing to a marked predominance of ipsilaterally ascending monoaminergic fibers are in good correlation with the telencephalic decreased concentrations of monoamines associated with ipsilaterally placed VTA and VMT lesions.

These morphologic changes (mostly retrograde cell degeneration), and the corresponding telencephalic monoaminergic decreased concentrations ipsilaterally to VMT lesions, are in good concordance with the associated parkinsonlike motor disturbances which are lateralized and, in the main, involve the contralateral limbs. The latter motor impairments, mainly characterized by resting tremor and rigidity or hypotonia, however, involve—in addition to the interruption of ascending monoaminergic pathways—other nervous structures which, as mentioned above, are concomitantly destroyed in VMT lesions. As a matter of fact the interruption of cerebello-rubral fibers reaching both divisions of the red nucleus, as well as cerebello-thalamic fibers such as those produced in the VMT type lesions, is apparently an important feature in the production of rigidity associated with the cogwheel phenomenon. The concomitant interruption of the corresponding rubro-tegmento-spinal tract, however, appears to result in hypotonia of the contralateral limbs instead of rigidity (4, 6).

On the other hand, the destruction of the small-celled division of the red nucleus or the interruption of the corresponding rubro-olivary fibers, such as encountered in VMT lesions, represents an important feature in the production of resting tremor. The marked decreased concentration of DA in the corresponding neostriatum, as mentioned above, is apparently the main feature in these parkinsonlike motor disturbances. Finally, akinesia or severe bradykinesia is observed only following extensive bilateral VMT lesions located at rostral midbrain level in the monkey (6). Under such conditions the main parkinsonian motor disturbances are represented by akinesia, resting tremor, and rigidity associated with the cogwheel phenomenon involving all four limbs. Moreover apomorphine administered in very low doses may transiently counteract all these motor disturbances (6).

Such extensive bilateral VMT lesions are associated with important decreased concentrations of monoamines in several telencephalic structures of both sides. The latter feature is most likely linked to the fact that rostrally located VMT lesions cause a more extensive interruption of ascending monoaminergic pathways than more caudally located midbrain VMT lesions. In this respect the parkinsonlike syndrome associated with bilateral rostrally located VMT lesions (6) is very similar to the parkinson syndrome induced by the administration of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) in the monkey. MPTP, a neurotoxic chemical agent which has been shown to produce parkinsonian condition in humans, produces highly selective damage of the dopaminergic cell population of the substantia nigra and an important reduction of the level of dopamine in the putamen and caudate nucleus (20–22).

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Role of the Nigrostriatal Dopaminergic Neurons in Mediating the Effect of Exogenous L-dopa in Parkinson's Disease

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The nigrostriatal dopaminergic projection is a key structure in the pathogenesis and therapy of Parkinson's disease. Degeneration of nigrostriatal neurons resulting in a dopamine deficiency state within the striatum is believed to be the primary cause of the clinical motor manifestations of this disorder. Furthermore, that projection is assumed to play an important role in mediating both the beneficial effects of exogenous L-dopa and the adverse reactions that emerge during long-term treatment in Parkinson's disease. Although L-dopa has been in wide use for almost two decades and is currently still the most potent available therapy in Parkinson's disease, we do not fully understand the mechanisms through which it produces benefit in afflicted patients. Contrary to earlier beliefs, it is now realized that these mechanisms are not simple, but rather highly complex.

The L-dopa Honeymoon. If treatment with L-dopa could produce long-lasting and stable improvement in parkinsonians, the precise unravelling of such mechanisms would probably have remained valuable only theoretically. However, after several years of treatment—the "L-dopa honeymoon"—continued long-term treatment with this drug may give rise to various limiting and sometimes devastating side effects, particularly a global decline in drug efficacy and dose-related random, unpredictable responses. The causes of these tolerance phenomena remain enigmatic. In fact, it is more than likely that the neurochemical effects of long-term treatment with L-dopa are far more complicated than those induced by short-term administration, particularly on the background of disease progression. In order to design better therapeutic strategies to prevent and counteract the decline in the efficacy of L-dopa, it is crucial to first clarify its mechanisms of action. Since the nigrostriatal projection may be central in the modus operandi of exogenous L-dopa, this review attempts to analyze the intricate involvement of that projection.

Nigrostriatal Neurons: General Features

The nigrostriatal dopaminergic projection is a major axis within the connective neuronal circuitry mediating basal ganglial function. It originates in the neuromelanin-containing dopaminergic nerve cell bodies in the A_9 region of the substantia nigra pars compacta. The axonal bundle ascends toward the corpus striatium, penetrates into and ramifies excessively within the caudate and putamen nuclei to form a dense network of nigrostriatal nerve terminals. These nerve endings contain all the neurochemical machinery required to synthesize, store, release, take up, and degradate the neurotransmitter dopamine. By forming numerous synapses with target postsynaptic striatal interneurons and/or efferent neurons, the nigrostriatal neurons exert a potent influence within the striatum despite their relatively small numbers (approximately 5,000 in rodents and 150,000 in humans).

Within nigrostriatal terminals, dopamine is synthesized by hydroxylation of the neutral amino acid tyrosine in a reaction catalyzed by the rate-limiting enzyme tyrosine hydroxylase. The

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formed L-3, 4-dihydroxyphenylalanine (L-dopa) is then decarboxylated to dopamine by the enzyme dopa decarboxylase (L-aromatic amino acid decarboxylase). Under normal physiologic conditions, a major fraction of the dopamine formed from endogenous tyrosine and L-dopa is stored within vesicles in the nigrostriatal nerve endings. A smaller portion of dopamine is nonvesicular and is present in the cytoplasm either in a free form or bound to macromolecules (for example, glycoproteins).

It is assumed that when the dopaminergic neuron fires, dopamine molecules are released from the vesicles into the synaptic cleft and react and activate postsynaptic dopaminergic receptors and thus transmit information downstream onto target striatal neurons. It is also believed that the vesicular dopamine represents the functional part, whereas the cytoplasmic dopamine is regarded as the nonreleasable, reserve compartment of the neurotransmitter. The synthesis and release of the vesicular-stored dopamine are controlled, regulated, and coupled to firing rates of the nigrostriatal neurons.

Thus, when discharge rates of the dopaminergic neurons are accelerated (as by treatment with dopamine receptor inhibitors such as neuroleptics or by electrical nigral stimulation), or suppressed (as by treatment with dopamine agonists), alterations in synthesis and release of dopamine take place. The coupling between nigrostriatal firing rates and dopamine synthesis and release is subserved, in part, through the enzyme tyrosine hydroxylase. This enzyme has a high affinity for its substrate tyrosine and when the neuron is quiescent, it converts only small amounts of tyrosine to L-dopa. However, when neuronal discharge rates are enhanced, the activity of the enzyme increases, its affinity for tyrosine declines, and more L-dopa is formed.

Several mechanisms govern the firing rates of nigrostriatal dopaminergic neurons. For example, after dopamine molecules are released into the synapse, they stimulate not only postsynaptic dopaminergic receptors but also inhibitory presynaptic autoreceptors located on nigrostriatal nerve terminals, thus signalling the neuron to decrease firing and dopamine synthesis and release. There are also various facilitatory and inhibitory neuronal circuits at the levels of both the nerve terminals in the striatum and the dendrites in the pars reticulata of the substantia nigra that modulate nigrostriatal discharge rates by activating receptors specific for their neurotransmitters which are present on these components.

Function. Although an enormous amount of information is currently available on the neurochemistry and neuropharmacology of the nigrostriatal neurons, very little is known about their function. It is generally agreed that this projection has an essential role in the control and regulation of movement. This notion is based on the common knowledge that when the nigrostriatal dopaminergic transmission is blocked pharmacologically (as by treatment with neuroleptics or reserpine) or by destruction of the projection (as in idiopathic, postencephalitic, or MPTP-induced parkinsonism), voluntary movement is suppressed. On the other hand, when nigrostriatal transmission is enhanced (as by drugs such as amphetamine or L-dopa or by electrical nigral stimulation), motor activity is accelerated. However, these paradigms are nonphysiologic, and it is totally unclear precisely how the nigrostriatal neurons are involved in the complex central mechanisms that govern motor activities under normal physiologic conditions.

This question becomes particularly difficult when electrophysiologic studies of this projection are considered. For instance, recordings of single-cell activity in active monkeys indicate that substantia nigra dopaminergic neurons exhibit low and more or less regular spontaneous discharge rates which remain unaltered and constant before, during, and after the performance of various motor activities. If such observations are valid, they suggest that nigrostriatal impulse flow and perhaps also dopamine release are unaffected by voluntary movement. In that case, it is possible that the regular, low-rate, intermittent, tonic release of dopamine in the striatum is not a primary generator or driver in the basal ganglia mechanisms that control movement. It may rather serve as a priming or tuning apparatus that sets the background on which other striatal neurons can act and transmit information required for the initiation and maintenance of movement.

To further compound this problem, it is unknown whether such modulatory action of dopamine on its target striatal neurons is achieved by intermittent pulselike stimulation or by continuous "inundation" of the postsynaptic dopaminergic receptors.

The Nigrostriatal Lesion in Parkinsonism And Its Neurochemical Consequences

The basic and crucial pathogenetic substrate in idiopathic Parkinson's disease is the progressive degeneration of the perikaria of the neuromelanin-containing dopaminergic neurons in the pars compacta of the substantia nigra, resulting in loss of their ascending nigrostriatal axonal projections, disappearance of the nigrostriatal nerve terminals within the caudate and putamen nuclei, depletion of dopamine in striatum, and suppression of the nigrostriatal dopaminergic neurotransmission. The causes of the death of nigrostriatal dopaminergic neurons in Parkinson's disease are unknown but may include, among others, viral, immune, genetic, and toxic factors or premature aging of these components (abiotrophy). There is evidence that additional dopaminergic pathways, such as the nigromesocortical and the nigromesolimbic, also degenerate in this disorder although to a lesser extent than that of the nigrostriatal projection. However, it is generally accepted that the motor clinical features of Parkinson's disease, mainly the rigidity and bradykinesia, are due to the nigrostriatal lesion and the resultant suppressed dopaminergic transmission within the striatum.

Support for this notion may be derived from studies in patients and monkeys with MPTP-induced parkinsonism. MPTP is a powerful neurotoxin that, when given systemically, produces in humans and primates an almost selective and irreversible destruction of the nigrostriatal projections. In parallel, it causes a clinical syndrome identical to that of the idiopathic "natural" Parkinson's disease.

Surprisingly, the first signs and symptoms of Parkinson's disease emerge only after a massive degeneration (approximately 80% of initial dopaminergic cell number) of the nigrostriatal projection. This may indicate that despite the relatively small number of dopaminergic nigral perikaria in the normal population (about 150,000), a substantial fraction of these cells may be redundant and an even smaller number may be sufficient to maintain the function of the nigrostriatal projection in the control and regulation of movement.

On the other hand, the timing of first signs could also suggest that powerful compensatory mechanisms are activated in the preclinical stages of Parkinson's disease to maintain this function despite the marked loss of nigrostriatal neurons. Studies in experimental animals and in postmortem tissues from patients with Parkinson's disease indicate at least two important neurochemical modes for such compensation.

First, when the nigrostriatal projection degenerates, the surviving neurons become hyperactive. They fire more rapidly and increase their rates of dopamine synthesis and release. In rats with partial nigrostriatal lesions of increasing severity that mimic the natural history of the progressive neuronal degeneration in Parkinson's disease, we found that nothing much happens when up to 60% of the system is destroyed. However, when the lesion exceeds this number, the remaining neurons become progressively more hyperactive. The mechanisms responsible for this phenomenon are not clear. When a nigrostriatal neuron fires, dopamine is released from the nerve terminals in the striatum and from dendrites in the substantia nigra pars reticulata. Since nerve endings and dendrites form a very dense network in their respective fields, perhaps dopamine molecules released from one nigrostriatal neuron can diffuse over short distances, reach and activate inhibitory autoreceptors located on terminals and dendrites of neighbouring neurons and thus suppress their firing rates. This could represent an additional mechanism that controls nigrostriatal discharge rates in the normal physiological conditions. When the nigrostriatal projection degenerates, the nerve terminals and dendrites become sparse with wider gaps between those originating from individual neurons. At this point, dopamine molecules released from a single nigrostriatal neuron at the levels of both the striatum and the nigra can no longer escape the metabolizing enzymes MAO and COMT and would be incapable of reaching and affecting neighbouring nerve endings and dendrites.

Thus, the surviving neurons may become disinhibited and hyperactive. Consequently, despite their small numbers, such neurons could compensatorily enhance rates of synthesis and release of dopamine which would be adequate for the correction of the suppressed nigrostriatal transmission in the preclinical stage of Parkinson's disease. Interestingly, those surviving neurons are not maximally hyperactive and their increased rates of dopamine turnover can be further enhanced by certain pharmacologic manipulations.

Another compensatory mechanism involves the postsynaptic dopaminergic receptors. When the nigrostriatal projection degenerates, postsynaptic dopamine receptors become supersensitive due to the dopaminergic neuronal denervation and reduced stimulation by their agonist neurotransmitter molecules. In rats with progressively severe partial nigrostriatal lesions, we found that when destruction rises to about 90%, receptor sensitivity is unaltered, probably because the surviving hyperactive neurons release sufficient amounts of dopamine molecules to stimulate the receptors. However, supersensitivity develops when the nigrostriatal lesions are marked and above 90%. Such supersensitive receptors can amplify the postsynaptic response to the small numbers of dopamine molecules released from the surviving presynaptic nigrostriatal terminals.

Correction of Dopamine Deficiency by Systemic Treatment with L-dopa

If the clinical signs and symptoms of Parkinson's disease are indeed due to faulty dopaminergic neurotransmission in the striatum due to degeneration of the nigrostriatal pathway with its terminal ramifications, correction of the absent or suppressed availability of dopamine molecules at striatal postsynaptic dopaminergic receptor sites might be beneficial. Systemic treatment with dopamine, the missing neurotransmitter itself, has no effect because dopamine cannot gain entry into striatal parenchyma through the blood-brain barrier. This is due to polarity of the molecule and the presence of the dopamine metabolizing enzymes monoamine oxidase (MAO) and catechol-O-methyl tranferase (COMT) within the endothelial cells of cerebral microvessels which degrade the neurotransmitter outside the blood-brain barrier.

Similarly, systemic administration of tyrosine, the first substrate in catecholamine biosynthesis, is not useful in significantly increasing dopaminergic neurotransmission in the parkinsonian striatum. Exogenous tyrosine can increase brain tyrosine levels, but the enzyme tyrosine hydroxylase constitutes a rate-limiting step in the conversion of the amino acid to L-dopa within nigrostriatal neurons. There is experimental evidence that the enzyme changes affinity to its substrate and produces more L-dopa and therefore more dopamine when the nigrostriatal neurons fire more rapidly. However, it is unlikely that this produces sufficient amounts of the missing neurotransmitter in the parkinsonian striatum. Furthermore, in the striatum, tyrosine hydroxylase is located almost exclusively within dopaminergic nerve terminals. In Parkinson's disease, the severe loss of nigrostriatal neurons is accompanied by parallel massive depletions of striatal tyrosine hydroxylase activity, so that almost no enzyme is available for handling exogenously administered tyrosine.

The major breakthrough in the treatment of Parkinson's disease was the introduction of large long-term oral doses of L-dopa. This immediate precursor of dopamine in the biosynthesis of catecholamines can gain access to the brain following systemic administration, increase dopamine levels and availability to postsynaptic dopaminergic receptors in the striatum, and correct the deficient nigrostriatal dopaminergic neurotransmission, and thus ameliorate the clinical parkinsonian signs and symptoms. Penetration of L-dopa into the striatum is made more effective by combined administration with peripheral dopa decarboxylase inhibitors that block the metabolism of exogenous L-dopa by the enzyme present in peripheral tissues and in endothelial cells of cerebral capillaries, where the enzyme acts as a blood-brain barrier trapping mechanism for circulating L-dopa.

Five crucial factors combine to form the substrate for the unique and extremely fortunate success of L-dopa therapy in patients with Parkinson's disease. First, exogenously administered L-dopa can penetrate the blood-brain barrier into striatal parenchyma. Second, dopa decarboxylase, the enzyme that converts L-dopa to dopamine—unlike tyrosine hydroxylase—is not rate-limiting in catecholamine biosynthesis. It has a low affinity for its substrate and is therefore capable of decarboxylating almost any amount of L-dopa to dopamine without being saturated. Third, despite the massive degeneration of nigrostriatal nerve terminals, sufficient residual dopa decarboxylase activity remains in the parkinsonian striatum to catalyze the conversion of exogenous L-dopa to dopamine. Fourth, the dopamine formed from exogenous L-dopa is functional; that is, it gains access to and stimulates striatal postsynaptic dopaminergic receptors. Fifth, in general, the postsynaptic dopaminergic receptors are not depopulated and remain in the parkinsonian striatum and are therefore capable of transmitting downstream the stimulation induced by the dopamine formed from exogenous L-dopa. Furthermore, systemic administration of L-dopa in Parkinson's disease does not elevate striatal dopamine concentrations to normal levels. Nevertheless, the low amounts of the L-dopa-derived dopamine are capable of restoring the suppressed nigrostriatal transmission because the postsynaptic receptors develop denervation supersensitivity. Therefore, their response to even small amounts of dopamine formed from exogenous L-dopa is enhanced.

Role of Nigrostriatal Neurons in Mediating Beneficial Effects of Exogenous L-dopa

A major difficulty in trying to explain the mechanism of action of L-dopa concerns the problem of where it is converted to functional dopamine molecules in the parkinsonian striatum after degeneration of the nigrostriatal nerve terminals. Based on the special characteristics described above that enable L-dopa to be effective, the central theory suggests that the conversion of exogenous L-dopa to dopamine takes place only within the surviving nigrostriatal neurons. This hypothesis leans on several facts and assumptions, mainly that (a) residual striatal dopaminergic nerve endings contain the enzyme dopa decarboxylase; (b) the surviving hyperactive nigrostriatal neurons are not only capable of accelerating the rates of synthesis and release of dopamine from endogenous tyrosine and the dopa formed from tyrosine hydroxylation, but also from exogenous L-dopa; and (c) the surviving neurons contain the vesicular system for storage of the dopamine synthesized from the administered L-dopa.

In the normal striatum, most of the dopa decarboxylase activity is contained within the nigrostriatal neurons. When the nigrostriatal projection is intact, systemically administered L-dopa is predominantly decarboxylated to dopamine in the striatum within the dopaminergic nerve terminals. This is supported by observations that in experimental animals with nigrostriatal lesions of progressive magnitude (produced by injections of various doses of 6-OH-dopamine into the nigra or of MPTP subcutaneously), the elevations in striatal dopamine levels induced by acute administration of L-dopa decline is parallel to the severity of the dopaminergic neuronal lesions. However, there is evidence that a small fraction of dopa decarboxylase activity is also located in other striatal components, such as serotonergic nerve terminals and nonaminergic neurons. Furthermore, these extradopaminergic dopa decarboxylase-containing elements are also capable of converting exogenous L-dopa to receptor-accessible dopamine molecules. This suggests that the surviving nigrostriatal neurons may not represent the only site for decarboxylation of systemic L-dopa in the parkinsonian striatum.

Can hyperactive surviving nigrostriatal neurons indeed utilize more exogenous L-dopa than normally firing neurons, and thus form sufficient amounts of dopamine to correct the deficient dopaminergic transmissions despite their very small numbers? Recent studies suggest that this is not the case. We found that when firing rates of nigrostriatal neurons are accelerated by neuroleptic drug administration or electrical stimulation of the nigra or are suppressed by treatment with direct dopamine agonists, formation and release of dopamine from exogenous L-dopa remain unaffected and similar to those in control animals given L-dopa alone. Electrophysiologic studies in animals with intact nigrostriatal projections indicate that systemic L-dopa suppresses the firing rates of dopaminergic neurons. It is therefore feasible, though not yet examined, that the dopamine derived from L-dopa and released into the synapse will stimulate presynaptic dopaminergic autoreceptors and attenuate or totally abolish the accelerated discharge rates of the surviving nigrostriatal neurons. Consequently, it is speculated that although in untreated parkinsonians the residual neurons are at a state of enhanced firing, long-term L-dopa may counteract this hyperactivity.

Is the dopamine formed from exogenous L-dopa stored within vesicles in the remaining dopaminergic nerve terminals as the dopamine derived from endogenous tyrosine hydroxylation? Currently available evidence does not support this possibility. First, synthesis and release of vesicular dopamine is normally coupled to firing rates of nigrostriatal neurons. Therefore, if the dopamine formed from exogenous L-dopa is packaged into the vesicles, acceleration or suppression of neuronal impulse flow would be expected to induce changes in release. But release is not affected.

Furthermore, we examined the striatal elevations of dopamine produced by an acute challenge of exogenous L-dopa in normal rats and in animals given reserpine to destroy the dopaminergic vesicles within the nigrostriatal nerve endings. We showed that the incremental increases of dopamine were similar in rats with an intact vesicular system and in those with massive destruction of the vesicular storage mechanisms. This suggests that unlike the dopamine formed from endogenous tyrosine and L-dopa, the major fraction of the dopamine derived from exogenous L-dopa is not stored within the vesicles. What now seems more likely is that it accumulates in the cytoplasm of nigrostriatal nerve terminals either in a free form or perhaps bound to macromolecules (no experimental evidence has so far been found). The latter fraction may represent a certain storage mechanism for this type of dopamine. This line of reasoning would also indicate that the utilization of the "endogenous" natural L-dopa (derived from tyrosine) and of the exogenous L-dopa by dopa decarboxylase, takes place in different subcellular compartments within the dopaminergic neuron. Perhaps there are two forms of the decarboxylating enzyme: one that is closely linked to tyrosine hydroxylase and directs its product toward the vesicular storage system, and another that produces dopamine molecules which remain in the cytosol.

All these considerations suggest that the dopamine formed from exogenous L-dopa does not gain entry into the functional releasable pool of vesicular dopamine and that its release from nigrostriatal terminals is not coupled and regulated by neuronal firing rates according to synaptic demand. We suggest that the "exogenous" dopamine simply builds up its concentrations in the cytoplasm and when this compartment is saturated, molecules spill out in an unregulated pattern into the synapse, where they reach and stimulate postsynaptic dopaminergic receptors and thus mediate the beneficial effect of administered L-dopa. This would also mean that activation of postsynaptic receptors by the dopamine formed from exogenous L-dopa is not induced via an intermittent pulselike form of neurotransmitter release (if this is indeed what occurs in the physiological state). Rather, as long as it is available, the spilled dopamine probably produces constant "bathing" of the receptors.

This pattern of unregulated spillage of nonvesicular cytoplasmic "exogenous" dopamine may be supported by an additional recent observation. When experimental animals are given an acute dose of L-dopa, there are very large increases in striatal levels of the dopamine metabolites DOPAC and HVA which exceed the elevations in dopamine itself. Surprisingly, MAO-B, the enzyme specific for dopamine degradation, is not present in the striatum within the nigrostriatal neurons but rather outside the nerve terminals, mainly in glial cells. By contrast, MAO-A, which metabolizes other monoamines, is present in nigrostriatal neurons.

The reasons for this enzymatic distribution are unknown and raise interesting speculations beyond the scope of this review. Briefly, under physiological circumstances, glial MAO-B may be responsible for metabolism of part of the dopamine molecules released from their vesicles into the synapse. Intraneuronal MAO-A may degrade the excess extravesicular cytoplasmic dopamine which originates from de novo production or reuptake of the neurotransmitter. It is likely that the vesicular-stored dopamine is protected from the cytoplasmic MAO-A. We found that when L-dopa is administered to experimental animals with drugs that selectively inhibit MAO-B (pargyline and deprenyl), the dopa-induced elevations in DOPAC and HVA are abolished. This supports the view that the dopamine derived from exogenous L-dopa gains access to the synapse, where it becomes accessible to the enzyme MAO-B. More important, we showed that combined administration of L-dopa with clorgyline, a selective MAO-A inhibitor, was as potent in preventing the striatal increases in DOPAC and HVA produced by L-dopa. This can be used as additional evidence that the dopamine formed from exogenous L-dopa in the nigrostriatal terminals does not enter into and is not protected from degradation by the vesicles and therefore readily falls prey to cytoplasmic MAO-A.

Role of Progression of Nigrostriatal Degeneration in Declining Efficacy of Long-Term L-dopa Therapy

L-dopa does not arrest the nigrostriatal degeneration, which continues relentlessly under the cover of therapy. One of the major hypotheses suggests that the declining benefit and fluctuations of response that emerge after prolonged treatment with L-dopa are due mainly to ongoing nigrostriatal loss and disease progression. Such a theory depends mainly on the claim that the surviving nigrostriatal neurons represent in the parkinsonian striatum the only site for decarboxylation of exogenous L-dopa and storage (in vesicles) of the formed dopamine, despite their exceedingly small numbers (about 10–20% of normal when first symptoms become apparent). However, when the nigrostriatal loss proceeds, a crucial point is reached beyond which the capacity of the parkinsonian striatum to adequately decarboxylate exogenous L-dopa and store the formed dopamine is lost.

There are many clinical and experimental lines of evidence for and against this theory not dwelt upon here. Note, however, that (a) there are other "extradopaminergic" striatal sites for utilization of exogenous L-dopa in Parkinson's disease, and (b) there may be other mechanisms responsible for tolerance to L-dopa, including receptor dysfunction, toxic effects of L-dopa, and pharmacokinetic faults. It is presently evident that the complex tolerance phenomena cannot be explained by a single mechanism, but rather by a combination of multiple factors. Nevertheless, it can be accepted that continued degeneration of nigrostriatal neurons may contribute to the altered responsiveness to L-dopa in parkinsonians through loss of an important decarboxylating reservoir and of dopamine storage (not necessarily in vesicles but probably in the cytoplasm). This mechanism might participate in the overall decrease in efficacy of L-dopa. Also, there may be short-lived small bursts of dopamine spillage into the synapse after each single dose of L-dopa. Owing to the diminished numbers of nigrostriatal terminals, storage of the formed dopamine is minimal. In addition, reuptake of the spilled dopamine probably declines drastically because of the sparsity of the terminals that contain the specific transport system for dopamine. Thus, most of the small amounts of dopamine molecules that reach the synapse following L-dopa administration will be metabolized by extraneural MAO and COMT. These latter factors could contribute to the development of response fluctuations.

Effect of Long-Term L-dopa Therapy on Progression of Nigrostriatal Lesion

The natural history of Parkinson's disease is characterized by progressive long-term deterioration that is unremitting. The rates of progression differ among affected subjects from slow to rapid, and may be predetermined in each individual. Causes of the nigrostriatal degeneration are unknown but may involve excess generation of cytotoxic free radicals that may be induced by environmental or endogenous MPTP-like neurotoxins or by premature aging. Free radicals formed during intraneuronal dopamine metabolism may also accumulate because of failure of the natural scavenging enzymatic defense systems or because of faulty production of neuromelanin. Oxidation of L-dopa may produce similar noxious agents.

Therefore, it may be speculated that long-term administration of L-dopa may constantly bombard and overload the surviving nigrostriatal neurons with exogenous L-dopa which, in turn, may produce excess free radicals. Such toxic substances might enhance the rates of nigrostriatal neuronal loss and consequently the progression of the disease. In such a case, and if further degeneration of nigrostriatal neurons indeed constitutes a major factor in the declining efficacy of chronic L-dopa, treatment itself could hasten the transition from smooth and stable responsiveness to the next period of benefit loss and response fluctuations.

Although we still do not know if this really takes place in parkinsonians, studies in experimental animals do not support such a theory. For instance, we found no evidence for damage to nigrostriatal dopaminergic neurons in normal mice fed very large doses of L-dopa daily for about 1.5 years. In addition, even when nigrostriatal neurons were made vulnerable in mice by pretreatment with the dopaminergic neurotoxin MPTP, chronic administration of L-dopa did not enhance the toxic effects of this agent and did not produce further damage to the dopamine neurons.

Fetal Nigral or Adrenal Medulla Cells and Improved Decarboxylation of Exogenous L-dopa

Recent studies indicate that following destructive lesions of the nigrostriatal projections by nigral injections of 6-hydroxydopamine in rats or by MPTP in primates, the resultant behavioral and neurochemical changes can be reversed by intrastriatal grafting of fetal nigral or adrenal chromaffin cells. These studies suggest that such transplanted cells can survive for long periods without being rejected, grow axons and probably establish functional synapses with target neurons within the striatum, thus restoring the deficient nigrostriatal dopaminergic neurotransmission. Currently available preliminary trials of autotransplantation of adrenal medulla tissues into striata of patients with Parkinson's disease yield conflicting results. At this stage it is too early to predict whether such an approach will be successful and beneficial, but it definitely represents another exciting breakthrough in the treatment of Parkinson's disease.

Much about this new paradigm is unknown. For instance, transplanted tissues could produce and release trophic growth factors that may promote survival and new sprouting of the remaining striatal dopaminergic neurons. Another intriguing question is how precisely these cells will produce, store, and release dopamine, and whether their turnover of dopamine will be governed by firing rates. Assuming that such cells can survive, grow neurites, and even reach and establish synapses with target neurons in the human parkinsonian striatum, they may, in all likelihood, remain deprived of the normal neuronal circuitry that connects with the nigrostriatal neurons and participates in the physiologic modulation of their firing rates. Lack of circuitry may lead to failure of this therapeutic approach unless transplanted cells are capable of firing regularly, or even irregularly, on their own and of releasing their vesicular-stored dopamine. Alternatively, these cells may not require firing as a prerequisite for dopamine release. The dopamine produced by these cells could simply accumulate in their cytoplasm and "ooze out" into the synapse.

Based on the above, we wish to suggest an additional theoretical indication for transplantation therapy in parkinsonians. The incapacitating decline in efficacy and response fluctuations following long-term L-dopa therapy may be due, in part, to a critical and irreversible loss of nigrostriatal nerve terminals or even other striatal components capable of decarboxylating exogenous L-dopa and of storing and releasing the formed dopamine. Intrastriatal grafting of dopa decarboxylase-containing fetal nigral or adrenal chromaffin cells in these patients may dramatically increase the decarboxylating capacity of the striatum and the conversion of exogenous L-dopa to dopamine. Such cells may store the formed dopamine in their cytoplams and release it even without the normal physiologic neuronal coupling between vesicular storage and neuronal firing. This sequence of events may "rejuvenate" the system and restore the initial beneficial smooth and stable response to exogenous L-dopa. Time will tell whether this speculation is valid.

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MPTP in Animal Models of Parkinson's Disease

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Several landmark discoveries made during the last 25 years have led to major advances in understanding and treating Parkinson's disease (PD). Carlsson discovered that dopamine was present in higher concentrations in the caudate nucleus, and that after depletion of this amine with reserpine, animals developed parkinsonian symptoms which were reversed by treatment with DOPA (1). Hornykiewicz (2, 3) has since shown that dopamine levels are low in the caudate nucleus of patients dying with Parkinson's disease, and suggested that treatment with L-dopa might benefit such patients. The clinical application of L-dopa for treatment of Parkinson's disease awaited development of a means to administer the large doses of DOPA required to control the parkinsonian symptoms (4, 5). Despite refinements of schedules of drug administration, use of peripheral decarboxylase inhibitors to potentiate the efficacy of L-dopa (6), and introduction of agents which stimulate directly brain dopamine receptors, pharmacologic treatment of Parkinson's disease is not completely successful. Although early symptoms may be controlled satisfactorily, the occurrence of "on-off" effects, dyskinesias and other movement disorders, and progressive loss of efficacy of L-dopa ultimately led to treatment failures.

The discovery in 1979 that self-administration by drug addicts of a contaminant produced during the illicit synthesis of a narcotic, alphaprodine, produces a parkinsonian syndrome in humans (7) gave new impetus to research on Parkinson's disease. The contaminant, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), was identified and subsequently found to produce, in primates, a motor disorder having all the major features of idiopathic Parkinson's disease in humans (7–11). This animal model of Parkinson's disease has not only provided a means of testing new approaches to drug and surgical therapy, but has also stimulated a search for environmental toxins which may contribute to the destructive process causing the death of dopaminergic neurons in the nigrostriatal system, and other less vulnerable neuronal systems. Here we review briefly our understanding of the MPTP toxin and advances fostered by the availability of the MPTP animal model of Parkinson's disease.

MPTP and Its Resemblance to Parkinson's Disease

Symptoms. Shortly after MPTP was first discovered (7) to be a potential neurotoxin, it was administered to rats, guinea pigs, and rabbits to test its effects on dopaminergic systems in the brain. Although systemic administration of MPTP damages the nigrostriatal dopaminergic neurons, resulting in acute behavioral effects, no parkinsonian features developed (12, 13). The animals recovered, and there were none of the long-term effects on the dopaminergic neuronal systems.

After the second encounter of parkinsonism in humans associated with MPTP (14), studies in primates were initiated, and it was soon apparent that MPTP administered to monkeys caused long-term changes in motor functions in these monkeys that included all the major features of Parkinson's disease: bradykinesia, hypokinesia, rigidity, postural and resting tremor, abnormal posture, decreased vocalization, and loss of facial

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expression (8). The degree of extrapyramidal involvement is dose-dependent and above a critical dose level, cumulative (15). Affected monkeys are unable to eat or drink without assistance and would die without extensive nursing care. As with human Parkinson's disease, these symptoms are readily reversed for a short interval (2–3 hours) by administering L-dopa or dopamine agonists (8).

Differences. There are some differences between MPTP-induced parkinsonism and Parkinson's disease. The latter is progressive, at varying rates for each affected individual. MPTP-induced toxicity appears to have three stages: acute, chronic, and compensatory. Markey (16) suggests that compensatory processes allow for some degree of recovery of function from the chronic parkinsonism in many MPTP-treated animals. In contrast to Parkinson's disease, dopaminergic neurons in the ventral tegmentum projecting to the mesocortical and mesolimbic dopaminergic systems are relatively unaffected by MPTP (17, 18). Moreover, the low brain levels of norepinephrine and serotonin noted in idiopathic Parkinson's disease are absent (2, 3, 19). Although the classic parkinsonian tremor is slow in frequency, involves distal muscles of the extremities, and is present at rest, the MPTP-induced tremor involves the proximal muscles of the extremities and is present when the animals maintain or take on a new posture. In MPTP-treated animals, there is little if any progression after the toxin has taken effect. Often, as indicated above, there is improvement to a more stable level.

Pathology. In the only human case of MPTP-induced parkinsonism which has come to autopsy, there was severe depletion of pigmented cells in the substantia nigra, and one eosinophilic inclusion body resembling a Lewy body was found (7). Similar eosinophilic inclusion bodies have been reported after systemic administration of MPTP to older squirrel monkeys (20). These inclusion bodies were detected only in areas (in the substantia nigra, dorsal motor nucleus of the vagus, nucleus basalis of Meynert, and dorsal raphe nucleus) where Lewy bodies are found in human Parkinson's disease (20). Thus, the pathologic changes in the brain of affected primates are very similar to those of human parkinsonism, even to the extent of formation of eosinophilic cytoplasmic inclusions resembling Lewy bodies in the substantia nigra. The nigrostriatal neurons are almost completely destroyed, whereas other neuronal systems are largely spared, although with repeated larger doses, particularly in older animals, other areas of primate brain may become involved (21).

Biochemical Characteristics. The biochemical consequences of dopaminergic neuronal destruction in the substantia nigra as the result of MPTP administration are the expected disappearance of tyrosine hydroxylase and of dopamine and its major metabolites (dihydroxyphenyl acetic acid [DOPAC], homovanillic acid [HVA]) in the striatum. In addition, both monoamine oxidase-A (MAO-A) and monoamine oxidase-B (MAO-B) activities are inhibited (22). MPTP causes increased serotonin levels in the median raphe and hypothalamus, while decreasing the 5-hydroxyindole acetic acid (5-HIAA) level. Whereas dopamine and HVA are diminished, norepinephrine release, together with levels of its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), are increased (23). In rhesus monkeys, the acute effects of MPTP injection cause a decline of HVA, MHPG, and 5-HIAA cerebrospinal fluid levels. In addition, norepinephrine metabolism is decreased, whereas in rats it appears to be increased (24). Chronically, dopamine synthesis and metabolism are substantially decreased in the nucleus accumbens and caudate nucleus of some species, including guinea pigs (12). Because MPTP has low affinity for both the dopamine and norepinephrine receptors, it is assumed that MPTP action is not a result of receptor stimulation. Rather its acute effects on serotonin are more consistent with activation of serotonin receptors.

Drug Treatment(s). L-dopa/carbidopa effectively reverses the symptoms, as do other agents which stimulate dopamine receptors. After L-dopa therapy to MPTP-induced parkinsonian in monkeys, local cerebral glucose utilization increases substantially in the caudate-putamen, globus pallidus, subthalamic nucleus, substantia nigra pars reticulata, and portions of the prefrontal cortex (25). These are all areas in the outflow pathways of neuronal activity regulated by the striatum and reflect dopamine receptor supersensitivity.

In C-57 black mice, MPTP administration causes severe depletion of striatal dopamine. This is consistent with some resultant impairment of open-field behavior. However, permanent significant degeneration of nigrostriatal neurons as evidenced by decreased amine accumulation or neuronal cell loss does not occur (26). The mouse, however, has been extremely useful for studies of the mechanisms of MPTP toxicity.

Mechanisms of MPTP Toxicity

Although not all of the mechanisms of MPTP neurotoxicity are defined completely, several factors are known to contribute to its target specificity and to species vulnerability. Such factors include the role of MAO in MPTP detoxification or activation, selective toxin uptake by targeted cells, reactive intermediate (see below) formation, possible interactions with neuromelanin, as well as the involvement of free radicals or concentration of the toxic compound in mitochondria, with consequent inhibition of mitochondrial oxidative enzymes. The ability of targeted neurons to repair damage or regenerate also is important in determining the effect of the toxin.

Studies of the distribution and metabolism of MPTP showed that the drug, which is lipid soluble, is readily distributed throughout the body, including the brain, since it easily penetrates the blood-brain barrier. However, MPTP is rapidly metabolized to its quaternary derivatives 1-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$) and 1-methyl-4-phenylpyridinium (MPP^+), which are not readily membrane permeable. MPTP may autooxidize by spontaneous disproportionation to form $MPDP^+$ and MPP^+, or may be converted by MAO-B to MPP^+ (Fig. 1). This can occur in brain mitochondria as well as in astrocytes, liver, kidney, and other tissues (27–29). The MPP^+ thus formed in the brain from MPTP can then become entrapped there and may accumulate in the substantia nigra (16, 30), where it can remain up to 20 days in monkeys but only a few hours in rodents (31). Although more toxic in older animals, the brain levels of MPTP or MPP^+ are not higher. In fact, MPTP is metabolized more rapidly in the older mice, possibly due to greater MAO activity that is concomitant with aging. It appears that MPTP-induced neurodegeneration is not due to greater MPP^+ levels, but rather to a greater sensitivity of older dopaminergic neurons to MPTP. When MPP^+ is administered intrastriatally in mice, it causes marked striatal dopamine depletion and significant behavioral disruption in the shuttlebox avoidance paradigm. L-dopa reverses both MPP^+-induced deficits (32).

Inhibition of MAO-B by pargyline or deprenyl can prevent MPTP toxicity (33). However, MAO-A inhibitors (for example, chlorgyline) offer no protection (34). It has also been shown that MAO-B inhibitors prevent MPTP-induced parkinsonism in monkeys, and inhibit MPP^+ formation in both mice and monkeys (16, 34, 35). This indicates that formation of MPP^+ is necessary for the deleterious effects following MPTP administration.

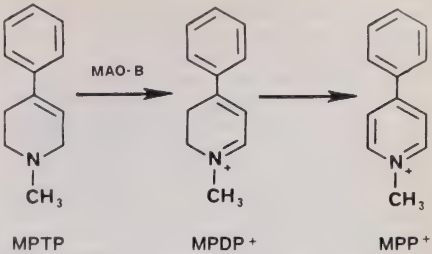

Fig. 1. MPTP conversion to its quaternary derivatives $MPDP^+$ and MPP^+.

Metabolism of MPTP to MPP^+ occurs where MAO-B is present throughout the body. Since MPP^+ does not readily penetrate the blood-brain barrier, metabolism of MPTP can provide protection for the brain. In rats, the capillary endothelium in brain tissue has higher levels of MAO-B, much higher than in mice, dogs, or primates (including humans). It has been suggested that this increased MAO-B activity in rat brain capillary endothelium accounts for the relative resistance of this species to MPTP toxicity. In this species, MAO-B serves as an enzymatic barrier by converting MPTP to MPP^+ which is unable to further penetrate the brain (36). When MPTP is injected intracerebrally in rats, there is widespread neuronal loss in the substantia nigra, ventral tegmentum, and dorsal raphe (37), suggesting that circumventing the blood-brain barrier will allow the toxin to act in rats.

MPP^+ formed in brain astrocytes apparently can escape into the extracellular fluid. From here, because of its affinity for both dopamine and norepinephrine uptake sites, it is concentrated in dopaminergic and noradrenergic neurons (38, 39, 40). The specificity of MPP^+ apparently is related to its concentration in catecholaminergic neurons. MPP^+ enters dopaminergic neurons via the dopamine uptake system and it appears that this mechanism is necessary to attain toxic intracellular levels. Specific dopamine uptake inhibitors (such as nomefensin) prevent the MPTP-induced neuronal damage (38, 41).

The high concentrations of MPP^+ attained (and retained) in dopaminergic and noradrenergic neurons may be important in the selective toxicity of MPTP, but do not account for the particular vulnerability of only some dopaminergic neurons. The presence of neuromelanin (42–45) has been implicated, since in those species in which the neuromelanin concentration is high, MPTP in relatively low doses causes death of the nigrostriatal dopaminergic neurons. MPP^+ can bind to neuromelanin, and this binding has been suggested as a means of maintaining high intracellular concentrations of the toxin which results in neuronal death (46). MPTP selectively kills melanin-containing neuronal cells in the substantia nigra of humans and primates. It has been shown that MPP^+, accumulated intraneuronally by the catecholamine uptake system, exhibits high-affinity binding to neuromelanin. It has been suggested that this bound MPP^+ may be stored and then gradually released, thus causing more severe neuronal damage in the substantia nigra (42, 43).

MPP^+ is also concentrated in mitochondria, where it inhibits electron transport at complex I, thereby interfering with NADH-linked pyruvate or glutamate oxidative metabolism (47). A possible mechanism for MPP^+ toxicity is redox cycling and generation of free radicals (31). The evidence for free radical generation was indirect, based on studies of paraquat, a compound causing tissue damage by free radical generation. Since paraquat is structurally and toxicologically similar to MPP^+, it was thought that MPP^+ too could catalyze superoxide and hydroxyl radical formation. However, Sinha et al. (48) have demonstrated that MPP^+ is a poor generator of free radicals. Moreover, a decrease in glutathione levels does not potentiate MPTP toxicity. Although MPTP causes glutathione depletion from the brain stem (49) and substantia nigra (50) of mice, there is no potentiation of MPTP toxicity when glutathione levels are lowered (51). In addition, neither MPP^+ nor MPTP toxicity is enhanced by antioxidants, whereas paraquat cytotoxicity is so enhanced (52).

MPTP and its metabolite MPP^+ both dose-dependently inhibit spontaneous and Fe^{2+}-induced lipid peroxidation in brain homogenates (53). This may be significant because, as indicated above, MPP^+ is actively taken up and accumulated by mitochondria in an energy-dependent, carrier-mediated transport process (54–56) causing a 40-fold increase in MPP^+ concentration.

It has been proposed that MPP^+ toxicity is mostly independent of free radical generation associated with oxidative metabolism. It is hypothesized that the mitochondria (site of MAO-B localization) is also the site for MPTP oxidation, and that the transformation of MPTP to MPP^+ by MAO-B plays a critical role in MPTP neurotoxicity in the substantia nigra. The initial uptake of MPP^+ by the dopamine transport system followed by mitochondrial accumulation would cause inhibition of NADH-associated respiration, decreased energy metabolism, and ultimately cell death. Neuromelanin accumulation may be possibly indicative of diminished oxidative capacity, and as such, an index of mitochondrial vulnerability to neurotoxins.

In summary, the several separate processes of MPTP metabolism to MPP^+, availability of MPP^+ to cells into which it is concentrated by a catecholamine uptake site, interaction with neuromelanin, accumulation in mitochondria, and inhibition of mitochondrial oxidative enzymes contribute to the focus of vulnerability of neurons of the nigrostriatal pathway to MPTP toxicity (Fig. 2). Other neurons may be attacked also, to varying degrees in different species; rapid metabolism of MPTP to MPP^+ outside of the blood-brain barrier may protect the brain from being damaged—as in rats or in the contralateral side of monkeys treated with MPTP by intracarotid injection.

Research Stimulated by Advent of MPTP Parkinsonism

Concepts of Etiology of Parkinson's Disease. The lack of epidemiologic evidence pointing to a genetic etiology for PD (57) is leading investigators to search for an environmental cause (for instance a toxin). MPTP toxicity has stimulated searches for environmental toxins which may be similar to MPTP or other substances which might be metabolized by MAO-B to an MPP^+-like compound. Since MPTP-induced parkinsonism and idiopathic Parkinson's disease are clinically nearly identical and the brain lesions are so similar, MPTP is well suited for use as an experimental model to study the pathogenesis and treatment of Parkinson's disease. All primates develop parkinsonian symptoms with progressive severity a few days after receiving MPTP injections. There are species differences in the degree of motor impairment, and within species, age and sex are major factors. Older females appear to be most vulnerable to MPTP toxicity. These variations, however, do not significantly alter the value of MPTP parkinsonian animals as a model for Parkinson's disease in humans.

Testing Efficacy of Therapeutic Agents. Because MPTP is rapidly metabolized, when administered directly into a monkey's carotid artery, only half

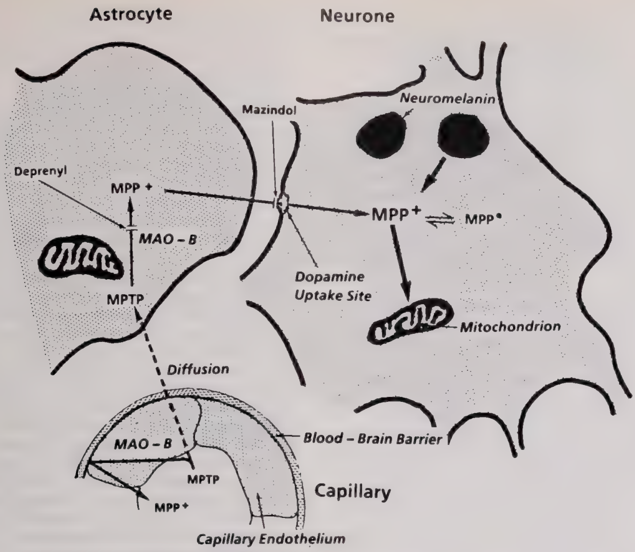

Fig. 2. Diagrammatic representation of separate processes influencing MPTP toxicity.

of the brain may be affected (58). Administered in this manner, the drug causes a unilateral parkinsonian movement disorder affecting the contralateral side of the body. The animal, during spontaneous motor activity, consistently circles toward the lesioned side—the side on which dopaminergic neurons of the nigrostriatal pathway are destroyed. On the treated side, the levels of tyrosine hydroxylase (the rate-limiting enzyme in dopamine biosynthesis) fall, dopamine and its metabolites virtually disappear, whereas the number of dopamine receptors on the chemically lesioned side increase. This results in a supersensitivity to dopamine and dopamine agonists. When the monkey is given L-dopa/carbidopa or apomorphine, it reacts by circling in the opposite direction, that is, away from the lesioned side. The onset and rate of circling are dose dependent and provide an index of drug efficacy. Thus, hemiparkinsonian monkeys may provide a useful means for predicting efficacy—time of onset, duration of effect, and magnitude of response—for new drugs.

Potential for Retarding the Degenerative Process. Since MAO-B inhibitors block MPTP toxicity and use of deprenyl, an MAO-B inhibitor originally administered to potentiate the effects of L-dopa/carbidopa was reported to prolong the life expectancy of Parkinson's disease patients (16, 27, 35, 59); use of this agent to retard the degenerative process is being explored. Antioxidants to prevent mitochondrial damage are also being examined.

Surgical Approaches to Therapy of Parkinson's Disease. The usefulness and possible mechanisms of brain or other tissue implants in reversing parkinsonian symptoms are being explored in MPTP-treated monkeys (60, 61). Parkinsonian patients' adrenal medullary tissue implanted into their own caudate nucleus have been reported to improve the disease symptoms to varying degrees. The mechanism of this reversal is actively being investigated at several medical centers.

In summary, four general questions remain to be answered: Is there an environmental neurotoxin involved in the pathogenesis of Parkinson's disease? Is selective species vulnerability to MPTP toxicity related to the development of Parkinson's disease? Can certain drugs (for example MAO-B inhibitors) which block MPTP destruction be useful in arresting the progression of Parkinson's disease? And finally, can the MPTP animal model of Parkinson's disease be employed to develop new treatments (drugs, implants) for PD as well as to provide basic data on the role of dopamine in brain function?

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Lessons from Stereotaxic Surgery Using Microelectrode Techniques in Understanding Parkinsonism

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Stereotaxic surgery for the extrapyramidal symptoms of parkinsonism dates back to around 1950, when pallidotomy for various kinds of involuntary movements was initiated almost simultaneously but independently in several parts of the world, including the United States, Sweden, France, Germany, and Japan. The effect of pallidotomy was mainly on rigidity and only transient on tremor. The target structure then gradually moved to the ventrolateral (VL) nucleus of the thalamus.

The effects of a surgical lesion in the thalamus on rigidity and tremor are marked, often dramatic, and sustained. With alleviation of these symptoms, accompanying motor difficulty —unskilled coordinative and delicate movement as well as slowness of movement—disappears immediately while the patient is still on the operating table, that is, within 10 to 20 seconds after the lesion is produced. These marked and immediate changes and accompanying improvement in the contralateral side of the body were observed in the earlier period of research as they are today. In many but not all patients, the overall effect continues for many years after surgery. In the author's series, the longest sustained abolition of rigidity is 27 years after pallidotomy, and the longest sustained abolition of both rigidity and tremor is 23 years after VL-thalamotomy, both in juvenile parkinsonians. Clearly, the effect of surgery on these symptoms is long-lasting when surgery hits the right target without excessively damaging the neighboring structures. However, symptoms other than rigidity and tremor—akinesia, emotional changes —may continue to progress, and as a result the patient's general capability in daily activities may worsen.

The surgery has beneficial effects because it interrupts the anatomic structures responsible for producing or carrying neural mechanism of rigidity and tremor. If the targeting and placement of the lesion in these structures are not precise enough, abolition of symptoms may be transient, lasting only a few weeks. Thus the critical aspect of the procedure is exactness in hitting the target lying at a depth in the brain. Development of the technique has principally focused on how to achieve much greater accuracy in each patient.

Technique of stereotaxic surgery is based on anatomic, radiologic, and physiologic study.

Anatomic and Radiologic Study. Three-dimensional coordinates of the target structure are referred to the intracerebral structures, which can clearly be visualized in the atlas of the sectioned brain and also on the radiogram of the ventricular system. These reference structures are the anterior and posterior commissures (CA and CP) or the foramen interventriculare of the third ventricle. Detailed anatomic atlases of the human brain have been prepared and published by Schaltenbrand and Bailey (1), modified later by Schaltenbrand and Walker (2), Spiegel and Wycis (3), Talairach et al (4), Dewulf (5), van Buren and Borke (6), and Andrew and Watkins (7).

Physiologic Study. However, even these atlases, usually prepared from the brain of a healthy young adult, cannot indicate the definite anatomic site of each structure in the brain of an individual patient, especially after pathologic changes in the brain. To overcome this difficulty,

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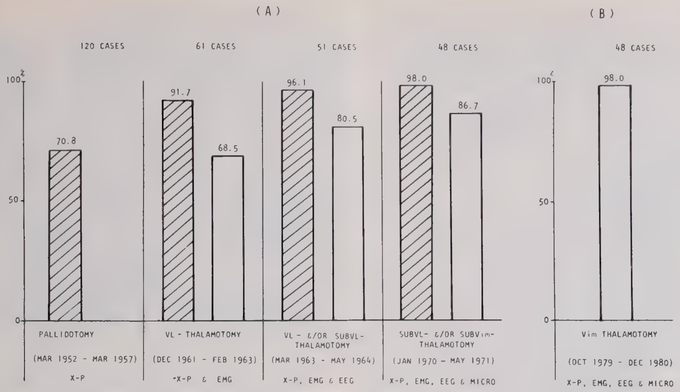


Fig. 1. Effects of various operative procedures on tremor in parkinsonism. Hatched bars, rigidity; solid white bars, tremor. X-P: radiologic control with PVG. EMG: observation of EMG effects of high-frequency stimulation of thalamus on motor activity. EEG: thalamocortical evoked potential. MICRO: depth recording with microelectrode. These are main guiding methods used in period indicated in parentheses. Numbers immediately over bars indicate effects in % of each procedure (pallidotomy, VL thalamotomy, sub-VL-thalamotomy, sub-Vim-thalamotomy, and Vim thalamotomy). *From Narabayashi (25). Part of figure labeled (A): reproduced from Fukamachi et al (10), by courtesy of the editors and publishers.*

several devices using neurophysiologic criteria were developed. Observation and analysis of the changes of symptoms for stimulation of target structures, such as tremor, rigidity, speech, or sensory symptoms are most commonly used. Recording and analysis of cortical evoked potentials for stimulation of the various thalamic subnuclei was introduced by Yoshida et al (8) to identify each subnucleus. Finally, recording of the unitary activity of the neuron in the deep-lying structures, especially of the thalamus, introduced by Albe-Fessard, et al (9), has been the most delicate and reliable way of identifying the detailed structures and their arrangement in the depth of the brain.

The many reports in the history of human stereotaxy offer detailed descriptions of each of the techniques. In the author's clinic (10), progress has been made in treating tremor surgically (Fig. 1).

Unitary Activity Recorded by Microelectrode

Through the stereotaxically inserted semimicroelectrode with a tip size of 7μ–10μ, the unitary neuronal activity (field potential) is recordable as a spike discharge from the various structures in the depth of the brain. Size, shape, and pattern of spike discharges differ in each nucleus, depending on the size, population density, and functional role of the constituent neurons (11). Analyses are made of these unitary activities and background discharges (noise level, the value indicating the level of overall electrical activities around the tip-electrode integrated for 2 msec). Because electrical activities of cells and of fiber are distinctly different, the border between the white and gray matter is clearly and easily recognizable (10). Each subnuclei of the thalamus exhibits a different level of noise, the ventralis intermedius nucleus (Vim) the highest, followed by the ventralis lateralis nucleus (VL; virtually synonymous with the ventralis oralis anterior, or Voa, and posterior, or Vop, nuclei in Schaltenbrand-Bailey atlas), the ventralis posterior nucleus (VP), and the centré median (CM) nucleus.

Vim Neurons. The Vim, the nucleus to be lesioned for alleviation of tremor, contains the largest neurons within the ventral thalamus (12)—approximately 45μ–55μ diameter (5), and also presents the large spikes and highest noise level within the ventral group of subnuclei. The Vim neuron also presents evoked discharges for peripheral natural stimulation of muscles or joints (11, 13–15). Therefore, if tremor exists in a part of the body, rhythmic stimulus of muscle stretching due to tremulous movement causes evoked tremor-synchronous rhythmic discharges in the Vim neurons. These proprioceptive neurons are delicately organized in somatotopic

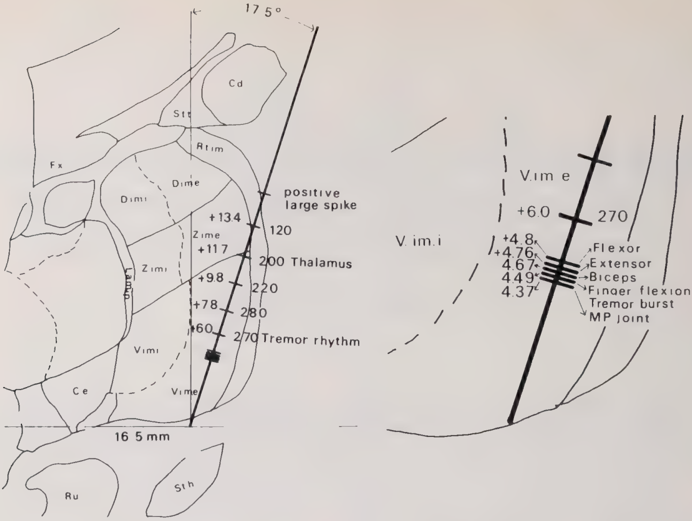


Fig. 2. At ventral part of right Vim, neurons receiving proprioceptive afferents are distributed in delicate somatotopic mosaic. Numbers to left of needle-track are distance in mm to tentative target point on baseline (CA-CP line). Numbers to right indicate noise level at each point.

fashion (Fig. 2). Within the Vim, leg-associated neurons are lateral, neurons associated with face and tongue are medial, and arm- and finger-associated neurons are in between.

Vim and VL in Relation to Tremor and Rigidity. Once the Vim is identified and located three-dimensionally, the neighboring structures are assumed to be the VL anterior to and bordering the Vim, the VP posterior, and the CM medial to the Vim. After confirming the anatomic sites of these subnuclei, high-frequency electrical stimulation (40–60 Hz, 1 msec and 0.2–0.3 mA) is given. With stimulation of the Vim, suppression of tremor is usual, although facilitation of tremor, without much change in rigidity, is also observable in a few cases. Cogwheeling is often increased. VL stimulation mainly causes an increase in rigidity and in the amount of tonic stretch reflexes on the surface EMG recording.

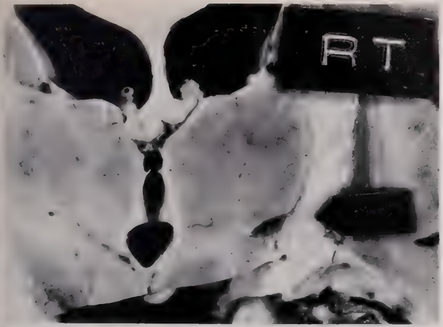
A selective small lesion of 3–4 mm diameter confined within the Vim mainly abolishes tremor sustainedly, whereas a lesion within the VL primarily eliminates rigidity (14, 16). With a VL lesion, tremor often disappears immediately but recurs within a few weeks. To treat both symptoms, the ventral portion of the VL and the Vim (Fig. 3) is the target, via either two small lesions in the VL and the Vim or a single lesion, slightly larger (4–5 mm diameter), involving both subnuclei.

Based on these analyses of a large number of cases, I have concluded that rigidity and tremor of parkinsonism have different anatomic substrates and neurophysiologic mechanisms.

Long-Term Results of Surgery

Newer, more sophisticated neurophysiologic surgery devices have brought stepwise improvement in sustained effects on tremor (Fig. 1). Clearly, the microelectrode technique achieves the most effective results. Recurrence of tremor and rigidity has been considerably reduced, and reverse effects of surgical invasion now seldom occur. Since detailed long-term observation of patients operated on is being described elsewhere (17), only a summary is given here.

Tremor Dominance. Patients with severe tremor that seriously affects vital daily activities (eating, writing, dressing) with various grades of rigidity have been dramatically improved by surgical treatment, when tremor is unilateral or asymmetrically distributed on the two sides of the body. In 16 of 21 cases (76%), improvement has been continuous for 3 to 8 years postoperatively, with a better ADL than preoperatively



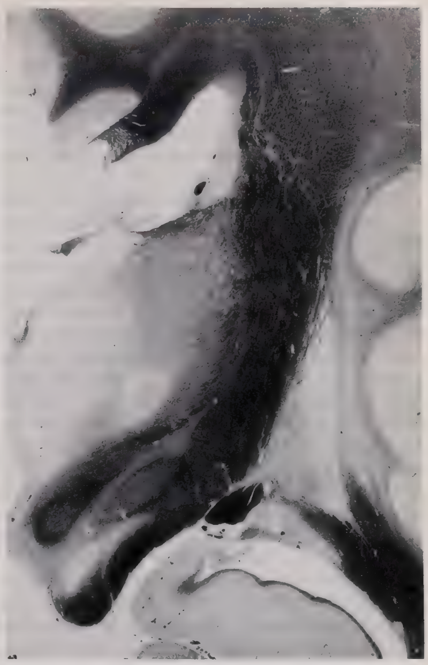


Fig. 3. **Above** Frontal section of brain of a female parkinsonian patient aged 69, who died of cancer two years after right ventral intermediate thalamotomy. Surgical electrothermocoagulation lesion was made around leg neuron. *From Narabayashi (14), reproduced by courtesy of the editors and publishers.* **Right** Frontal section of brain of a female parkinsonian patient who died of pneumonia at age 52, 3 ½ years after right-sided Vim & VL thalamotomy. Surgery improved movements of arm and fingers better than leg. Coagulation lesion was produced around neurons responding to wrist movement.

(Table 1). In 3 of 21 cases (14%), ADL was similar to preoperative levels because of moderate progression of other side symptoms. A total of 90% of the cases clearly had ADL levels similar to or better than preoperative levels and are working almost normally in their jobs or their housework.

Hemiparkinsonism for More Than 4 Years. If unilateral rigidity and tremor are not satisfactorily treated by medicine, a surgical procedure on the contralateral thalamic subnuclei is the treatment of choice. In my clinic we have achieved good long-term results for such patients whose ADL was similar to patients with tremor (Table 2), including seven patients free of symptoms on the other side who postoperatively were drug-free (Table 3). If in the postoperative period slight symptoms develop on the other side, however, the patient presents the picture of other-side hemiparkinsonism.

Asymmetric Symptoms. Patients with asymmetric bilateral rigidity and/or tremor usually also have akinesia. Medicinal dosage is determined by the effect on the more severely affected side, usually requiring a high dose of levodopa. After unilateral surgery on the side with the most severe symptoms, the dosage can usually be reduced to almost half; better performance in ADL can be reached with a lowered dose.

Long-term postoperative results for this group (Table 4) show the percentage of ADL grades C and D (together, 22%) to be higher than in the tremor-dominant and the hemiparkinsonism groups, indicating that surgery does not influence the progressive worsening of akinesia, although rigidity and tremor are sustainedly controlled on the previously severer side.

Bilaterally Operated-on Patients. Experience with bilateral surgery indicated a slightly greater tendency than unilateral surgery to produce reverse effects on speech and in the emotional sphere. Introducing the microelectrode technique, however, produces a much smaller, precisely placed lesion. The possibility of producing a reverse phenomenon is thus minimized, if selection of cases for surgery is careful.

Bilateral operations were performed on 25 patients; detailed evaluation of ADL in these patients is given in my original report (17). In this group (Table 5) all patients achieved postoperative independence in ADL—17 patients becoming close to normal in jobs and social life (A grade) and 8 becoming independent at home (B grade); none were classed as C or D grade. Three became drug-free.

When the long-term results of the operated-on cases were analyzed, it became apparent that all of the bilaterally operated-on cases could be classified into two groups: tremor-type PD and juvenile parkinsonism (JP) (18, 19). None of the patients had severe primary akinesia, although many had relative rigidity and secondary akinesia due to rigidity. Bilateral surgery, usually undertaken at intervals of more than one year, produced no side effects in any patient, principally because of the limited, tiny lesion exactly confined within the ventral portions of the Vim and the VL.

In patients with tremor, tremor on both sides disappeared and only a small dose of levodopa was needed. Even the highest dose of levodopa could not control tremor before surgery.

The juvenile parkinsonians had no levodopa-induced dyskinesia postoperatively on either side of the body—one of the major difficulties in treating JP cases. Up-down oscillation caused much less difficulty postoperatively, because rigidity with or without tremor in the down phase of drug effect has disappeared and only akinesia needed drug treatment. Two of these bilaterally operated-on JP patients and one tremor-type patient became totally drug-free, allowing normal social and work performance.

Lessons in Understanding Parkinsonism

Tremor and Rigidity. Tremor and rigidity have been located on different anatomic substrates, tremor in the Vim and rigidity in the VL.

Efferent projections from the internal segment of the pallidum to the thalamus enter the VA and the VL, but not the Vim. I have reported that a stereotaxic lesion in the internal segment of the pallidum eliminated rigidity but not tremor (20, 21). Tremor was seen to be abolished only temporarily, but the phenotype of tremor can be modified by the change of underlying rigidity (21). Rigidity is therefore considered to be a symptom arising as the pallidum is released from striatal control.

The Vim is a subnuclei just anterior to the VP, the sensory relay nucleus, and posterior to the VL (23). It receives the proprioceptive sense from the peripheral muscles and joints, and also the inflow from the deep cerebellar nuclei with a few fibers from the main vestibular nucleus. The Vim, clearly a structure different from the VL in both fiber connection and cytoarchitectonics, is interpreted to be concerned with the generation or regulation of tremulous movement. The tremor-generating mechanism and/or its circuit remains unexplained, however, and the question remains whether the Vim is the center of rhythmic tremor generation, even though it can be considered a key structure of the phenomenon (24, 25).

TABLE 1

Long-Term Results in Tremor-Dominant Patients Operated on Unilaterally

Grade	Year of surgery (no. of cases) 1977 (0)	1978 (2)	1979 (6)	1980 (3)	1981 (8)	1982 (2)	Total (21)
A	0	2 – (one died of heart attack)	3 –	3 –	7 – (one died of heart attack)	1 –	16 –
B	0	0	2 –	0	0	1 –	3 –
C	0	0	1 –	0	0	0	1 –
D	0	0	0	0	1 +	0	1 +

A: Better ADL than preoperatively; tremor completely stopped on operated side, normal living conditions at jobs or in active housekeeping; progression of tremor on unoperated side nil or slight.

B: Complete alleviation of tremor on operated side; improvement in ADL poorer than in A and similar to preoperative period because of progression of tremor on unoperated side.

C: No tremor on operated side, but disability increased and ADL worse than preoperatively due to progression of akinesia and of tremor on other side.

D: Tremor not controlled by surgery; akinesia generally worse; deterioration in ADL.

–: Tremor remains eliminated.

+: Tremor could not be controlled even at time of surgery.

The foregoing relationships are outlined in Fig. 4. In 1967, Smith (26) found, from the patho-

TABLE 2

Long-Term Results in Patients with Hemiparkinsonism

Grade	Year of surgery (no. of cases) 1977 (5)	1978 (10)	1979 (4)	1980 (7)	1981 (6)	1982 (5)	Total (37)
A	2	5	4	6	5	4	26
B	1	3	0	1	0	1	6
C	2	2	0	0	0	0	4
D	0	0	0	0	1	0	1

A: Better ADL than preoperatively; no rigidity nor tremor on operated side, no or slight symptoms on other side.

B: Almost same ADL as preoperatively at time of survey. Operated side, only slight symptoms; symptoms on other side developed.

C: Worse ADL than preoperatively; symptoms on other side and akinesia increased.

D: Not benefited at time of surgery; much deteriorated at time of survey.

TABLE 3

Hemiparkinsonian Patients Medicine-Free Postoperatively and at Survey

Case	Year of surgery	(Postop. period, yrs)	Age at onset (yrs)	Duration of illness (yrs)
1	1979	(6)	37	6
2	1979	(6)	57	4
3	1980	(5)	61	5
4	1980	(5)	59	4
5	1981	(4)	43	4
6	1981	(4)	50	5
7	1982	(3)	45	4

logic verifications, that in patients whose rigidity was improved, the surgical lesion had been in the various parts of the pallido-thalamic projection, whereas in patients whose tremor was abolished, the lesion was more posterior. This pathologic observation seems to fit the present clinical analysis.

Levodopa-Induced Dyskinesia. Levodopa-induced dyskinesia in extremities does not appear on the previously operated side of the body. It was also described by Hugh et al (27). It is eliminated by surgery on the VL, but not on the Vim, as analysed and reported by the author et al (28). This symptom depends on the pallidum-VL projection as rigidity does, and both symptoms underlie the striatal control. When nigrostriatal DA is deficient, rigidity appears and when an overdose of levodopa or supersensitivity of the striatal neuron to DA exists, levodopa-induced dyskinesia becomes manifest. Both rigidity and dyskinesia can be eliminated completely and sustainedly by the same surgical lesion within the VL. This suggests that these two symptoms derive from the mechanism arising in the same anatomical structures, and manifesting differently depending on the different level of DA in the nigrostriatum.

TABLE 4

Long-Term Results in Patients with Asymmetric Symptoms

	Year of surgery (no. of cases)						
Grade	1977 (3)	1978 (9)	1979 (10)	1980 (10)	1981 (18)	1982 (18)	Total (68)
A	1	4	5	6	8	15	39
B	1	1	3	3	4	2	14
C	1	2	1	1	6	1	12
D		2	1				3

A: Markedly benefited by surgery; ADL remains improved over preoperative status (independent, working in jobs or active in housekeeping). Disability score at survey, grades I and II or early III.

B: Well benefited by surgery in immediate postoperative period; slowly worse afterward. At time of survey, disability score mostly grade III or early IV, similar to preoperative grade under almost same dose of medicine.

C: Modified relatively by surgery, but at time of survey worse than preoperatively and deteriorated, mostly due to progression of disease. Disability score at time of survey mostly IV.

D: Did not benefit from or not influenced by surgery acutely or subacutely. Due to progression of disease, disability score mostly IV or V.

Three Types of Akinesia. Akinesia is a common term often vaguely used to describe the state of patients presenting slow and unskillful movement, or nearly complete lack of movement, starting from the masking of facies, slow and low voice, unclearness of speech, poor arm-swinging and axial movements, difficulty in locomotion and so on. Barbeau (29) reported that akinesia often remained even after elimination of muscle rigidity by stereotaxic surgery. This result implies that akinesia is a symptom independent from rigidity and tremor in PD.

Akinesia secondary to rigidity: Slow or unskillful movement, especially difficulty of coordination in arm movement, is almost always improved with amelioration of rigidity in 10–20 seconds after placement of the lesion on the patient. This type of difficulty thus seems better referred to as "akinesia secondary to rigidity," which I have named the "first type" of akinesia.

Primary akinesia: The second type of akinesia is perhaps best described as "primary akinesia" (30, 31); it cannot be influenced either for better or for worse by diminution of rigidity, and thus is not secondary to rigidity. Apparent here is the poverty or lack of movement, adeptly described by Martin (32). Difficulty in performing two different movements simultaneously may relate to this type of akinesia. Careful observation suggests that this type of akinesia predominantly affects proximal or truncal movement or locomotion, although it also appears in wrists, finger, or facial movement.

Both these types of akinesia greatly improve with levodopa therapy and are therefore interpreted as being due to striatal DA deficiency. However, since stereotaxic surgery precisely interrupts a part of the main exit pathway from the striopallidum, eliminating rigidity at the ventromedial part of the pallidum internum or at the VL of the thalamus, the second type of akinesia can be assumed not to be related to the rigidity-conducting pathway. To understand the generating mechanism of primary akinesia, the structures other than the striopallidum, the remaining part of the striopallidum, or the pallidum-VA projection, which are not included in the surgical lesion, should be studied carefully. The fact that the effect of levodopa is the same on the operated-on and the unoperated-on side, an effect also described by Hughes et al (27), may also indicate that the first and second types of akinesia have different morphologic bases. From these observations, the results of stereotaxic thalamotomy suggest an important question on the nature of primary akinesia.

Freezing akinesia: A third type, "freezing" akinesia, often occurs at the start of movement, especially of gait and speech (33). I, with colleagues, have analyzed this phenomenon as presumably due to deficiency of norepinephrin (NE) in the CNS (34). L-threo-3,4-dihydroxyphenylserine (L-threo-DOPS), the industrial precursor of NE, has been found useful in relieving this specific symptom (35).

Nature of Progression of the Disease. When the author became confident of exactness in the target of surgery, a number of questions arose. Since postsurgical improvement in levels of ADL is found to be sustained for 3–8 years postoperatively, even in some patients for 10–20 years, the nature of progression of Parkinson's disease and juvenile parkinsonism (JP) needs examination.

Most of the highly successful patients are bilaterally operated on, with satisfactory elimination of rigidity and tremor on both sides of the body. Also, most have either tremor-dominant disease with minimum primary akinesia or juvenile disease. In other words, persons with a minimum grade of primary akinesia can maintain long-lasting improvement in ADL when alleviation of rigidity and tremor are satisfactorily achieved. Furthermore, rigidity and tremor may not reappear when the structures necessary for their production are adequately destroyed. The most crucial symptom in the postoperative progression of disability, therefore, seems to be the presence and downhill course of primary akinesia, which is minimum in juvenile parkinsonism and patients with tremor.

JP has been found to be slower in progression than classical Parkinson's disease by the author and his colleagues (18, 19). Even in slowly progressing JP, however, the long-term (10–20-year) course is downhill. There has never been a case of spontaneous recovery. Although the course for certain bilaterally operated-on juvenile parkinsonians appears stationary, in 10–20-year follow-up slight deterioration, including start-hesitation or freezing, slight slowing, loss of skill in motion, and unsteady postural control definitely occurs. However, differentiating disease course from the results of aging and a conservative life style is sometimes difficult. Two juvenile parkinsonism patients monitored began to show freezing in gait without noticeable increase of rigidity, which was relatively improved by L-threo-DOPS.

This difference in speed of progression between JP and PD may hold the key to understanding the process of parkinsonism and of PD. Careful observation and long-term follow-up study of human cases of MPTP-induced parkinsonism, which seems similar to JP in clinical picture and course (36), are expected to provide some clue to the solution of the problem. Interpretations of and research on the progression of the disease process should center on clarifying the exact nature of "primary akinesia."

TABLE 5
Results in Bilaterally Operated-on Patients

	A (drug-free)	B	Total
Tremor	9 (1)	5	14
Juvenile parkinsonism	8 (2)	3	11
Total	17	8	25

A: Almost normal in job & social life.
B: Independent at home, full home work.

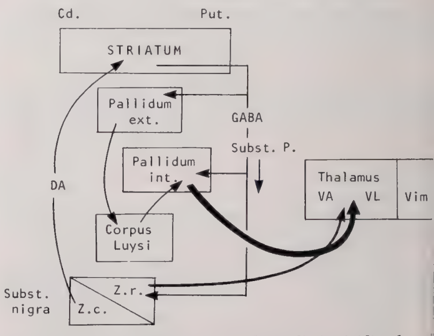


Fig. 4. Functional relation of basal ganglia in rigidity, levodopa-induced dyskinesia, and tremor, as understood from analyses of results of stereotaxic surgery using microelectrode.

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Options for the Etiology of Parkinson's Disease: The Association with Dementia

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In this discussion of the etiology of Parkinson's disease, emphasis will be placed on its association with dementia, and the common thread linking Parkinson's disease and Alzheimer's disease—that they represent an exaggeration of age-related trends of deteriorating motor and intellectual function respectively.

Parkinsonism and dementia are syndromes that have many causes. Idiopathic parkinsonism (Parkinson's disease) and idiopathic dementia (Alzheimer's disease) occur predominantly in late life, and coexist in the same individual, with a higher than random frequency. Furthermore, many of the clinical, physiologic, biochemical and morphologic changes of Parkinson's disease and Alzheimer's disease are seen in minimal stages as a manifestation of normal aging of the nervous system (1). Here "normal" is taken to mean the average findings in a population of a defined age. This interpretation is in keeping with the usual dictionary definition of normality, and distinct from the concept of an "ideal" or "super" selected group; unfortunately the latter usage has crept into the literature on aging and leads to much confusion. The concept of what constitutes normal aging is not just a semantic quibble, for the understanding of normal aging is the cornerstone upon which hypotheses of degenerative disease of late life must be built.

The epidemiology of idiopathic parkinsonism is relevant to any search for its etiology. Since twin studies indicate that genetic factors are unlikely to play a major causal role, local differences in incidence and prevalence are likely to derive from environmental factors. What is known of differences in the distribution of the disorder? First, idiopathic parkinsonism is less frequent in China by 50% (2) and in Japan by 60%–65% (3). Second, there is a north-south gradient in the United States, the disorder being commoner in the north (4), similar to that for multiple sclerosis; a similar trend of increased frequency has been claimed to correlate with distance from the Equator in Sweden (5). Finally, the occurrence of idiopathic parkinsonism in African blacks appears to be far less than the comparable figure for whites, the difference approximating to ninefold, which is much more striking than any other epidemiological discriminating factor identified hitherto (Cosnett and Bill, personal communication).

No adequate explanation is yet available for these findings, but they clearly prompt speculations on the possible relevance of differences in the distribution of infective diseases, and geographic variations in dietary habit.

The factors linking parkinsonism and dementia with aging can be presented as a series of relevant observations falling into four categories: similarities between normal aging, idiopathic parkinsonism, and idiopathic dementia; associations between parkinsonism and dementia; latency between exposure to risk factors and onset of symptoms; animal studies.

Similarities between Normal Aging, Idiopathic Parkinsonism, and Idiopathic Dementia

Neuronal Loss. Although some populations of neurons survive aging without significant loss (for instance the oculomotor, trochlear and facial nerve nuclei), the regions which display maximal cell death in idiopathic parkinsonism (zona com-

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pacta of a substantia nigra) and idiopathic dementia (nucleus basalis of Meynert) also undergo substantial attrition with normal age (6). The normal rate of loss of nigral neurons appears to accelerate after the age of about 60 years (7).

Biochemical Changes. The biochemical correlate of the normal decline in numbers of dopaminergic cells in the substantia nigra is a falling concentration of striatal dopamine with advancing age. This occurs at an increasing rate in late life (8).

Pathologic Changes. The characteristic pathologic finding in idiopathic parkinsonism is the presence of Lewy bodies, and in idiopathic dementia the corresponding features are neurofibrillary tangles and senile plaques. Lewy bodies, tangles, and plaques all occur with increasing frequency in progressive aging of normal brains.

Physiological Changes. Long latency stretch reflexes characteristically become more prominent with advancing age. These reflexes have abnormally large amplitude in idiopathic parkinsonism (9).

Clinical Changes. Rapid alternating limb movements are impaired in the elderly. Similar changes are seen more obviously in idiopathic parkinsonism. Comparable relationships exist for the stooped posture, shuffling gait, increase in muscle tone, paresis of ocular convergence, and paresis of upward conjugate gaze. Similarly, Alzheimer's disease is clinically an exaggeration of the deterioration of intellectual ability that normally occurs in late life.

Associations between Parkinsonism and Dementia

Idiopathic Parkinsonism and Idiopathic Dementia. Although there is controversy over whether the dementia that occurs in association with idiopathic parkinsonism is the same entity as Alzheimer's disease, it does seem relevant that some 10%–20% of patients with idiopathic parkinsonism do have idiopathic dementia (10). Some patients whose initial symptom is intellectual deterioration also progress to develop bradykinesia, rigidity, and tremor.

The Neurologic (ALS-PD) Complex of Guam. This disorder generally has a clinical picture of either motor neuron disease (ALS) or a combination of parkinsonism and dementia (PD).

Pugilist's Encephalopathy. The syndrome of progressive neurologic deficits that follows repeated head trauma in boxers comprises dementia and parkinsonism.

Histologic Correlations. Although the Lewy body is characteristic of idiopathic parkinsonism, it also occurs with more than normal frequency in idiopathic dementia (11). Neurofibrillary tangles, one of the typical findings in idiopathic dementia, can also be the dominant histological feature of idiopathic parkinsonism (12).

Latency between Exposure to Risk Factors and Onset of Symptoms

Another feature linking parkinsonism and dementia to aging is the observation that in certain patients there seems to be a long latency, lasting up to several decades, between exposure to a risk factor and the appearance and progress of symptoms.

ALS-PD Complex of Guam. The etiology of the ALS-PD complex of Guam is likely to involve consumption of food products deriving from *Cycas circinalis,* which grows in profusion on the island (13, 14). Garruto et al (15) have reported on Guamanians who left the island to settle in California; some developed the ALS-PD complex up to 34 years after emigrating from Guam.

Pugilist's Encephalopathy. There are cases of the parkinsonism-dementia syndrome of pugilists in which the onset and progression of symptoms occurred over 20 years after giving up boxing (16).

Postencephalitic Parkinsonism. The pandemic of encephalitis lethargica left many patients with parkinsonism immediately after the acute illness resolved. However, there was also a substantial proportion of patients whose parkinsonism did not appear for several years, and there was a higher than normal prevalence of clinical features resembling idiopathic parkinsonism appearing several decades after the encephalitis (17). Note also that young patients who developed postencephalitic parkinsonism were relatively stable for many years, but in late life, their neurological deficits progressed (personal observation).

Familial Parkinsonism. A recent report of familial aggregations of idiopathic parkinsonism has revealed a trend for parent and child to develop symptoms at approximately the same time, with an age difference averaging 25 years (18). The low concordance rate of idiopathic parkinsonism among identical twins indicates that most cases of this disorder must be of environmental origin (19). Since the environment ceased to be shared by parent and child for many years prior to the onset of symptoms, this observation may also be construed as evidence for the existence of a significant latency between cause and clinical expression of disease.

Animal Studies

6-Hydroxydopamine in Rats. One animal model of parkinsonism is the rat with nigral lesions induced by direct injection of 6-hydroxydopamine. In such animals, the motor deficits progress as the rats become older (20).

MPTP in Mice. Intraperitoneal administration of methylphenyltetrahydropyridine (MPTP) in mice results in striatal dopamine depletion. Young mice recover from this effect, but the neurons of older mice do not (21).

MPTP in Monkeys. Another model of parkinsonism is the monkey injected with MPTP. The lesions in such animals resemble idiopathic parkinsonism more closely if the injections are carried out in elderly animals. Compared to young monkeys, the older animals manifest loss of neurons from the locus ceruleus, and inclusions resembling Lewy bodies have been reported (22).

Conclusions and Summary

Conclusions. From the evidence cited, associations can be inferred between idiopathic parkinsonism, idiopathic dementia, and normal aging of the nervous system. What do these associations mean?

1. It is possible that subclinical damage to the substantia nigra or nucleus basalis (or both) may lead to progressive symptoms many years later because these regions are particularly vulnerable to normal aging. Crucial to this concept is the importance of the compensatory capacity of the nervous system, which means that the surviving neurons inherit a greatly enhanced functional responsibility in senescence. Because of this compensatory adjustment, the loss of each neuron at the age of 70 years would be anticipated to have a far greater functional impact than death of the same neuron in a young adult.
2. A slightly different explanation can be developed from the premise that neurons may be damaged in such a way that their vulnerability is increased to whatever causes normal aging.

Evidence relevant to both proposals derives from studies on the natural history of idiopathic parkinsonism at different ages. A careful study was performed by Dejong and Burns (23) before the complexities that evolved to obscure the issues as a result of the advent of levodopa. Dejong and Burns showed that the rate of progress of clinical deficits was some fourfold faster in patients who developed idiopathic parkinsonism late in life, compared with young patients. This finding is certainly in accord with the notion that the accelerating normal attrition of nigral neurons in senescence might contribute to the appearance and progression of symptoms.

Summary. The concepts discussed here allow considerable heterogeneity of factors that may cause parkinsonism and dementia including, for example, subclinical neuropathologic damage induced by a variety of toxins or infective agents. Following the recognition that MPTP produces lesions and biochemical changes in the brain very similar to those of idiopathic parkinsonism, it has become established that at least 5 other pyridines can also damage the nigrostriatal pathway. MPTP can be compared to penicillin in that both are "pioneer" compounds discovered to have unexpected biological properties; subsequent study of congeners established a series of substances capable of similar actions.

It is entirely conceivable that parkinsonism and dementia may result from a wide range of related or unrelated causes, just as meningitis may derive from bacteria, viruses, fungi, protozoa, or chemicals. Whatever the etiology, it is likely that there is a "dose-response" relationship such that a higher "dose" leads to clinical expression of disease with a shorter latency, and a lower "dose" may only culminate in clinical deficits when superimposed upon the normal age-related attrition of neurons that is prominent in the substantia nigra and the nucleus basalis. The interaction between an exogenous agent and a host factor would be analogous to the need for organisms of low pathogenicity to operate in an immunologically compromised subject to produce disease.

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Continuous Dopaminergic Stimulation in The Management of Complicated Parkinson's Disease

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For many years, research has been devoted to the comprehension of the side effects of long-term levodopa treatment of parkinsonism. "On-off" fluctuations and dyskinesias, in fact, occur in a large number of patients on levodopa therapy. The younger the patient, the higher is the incidence and severity of such symptoms. Although oscillations in motor performances have not yet been seen in de novo patients treated with synthetic ergoline dopamine(DA)-receptor agonists, these compounds are not very effective in complicated conditions, only partially improving on-off fluctuations when administrated in association with levodopa. Because of fluctuations, many patients may be compelled to cram all their daily tasks into two or three half-hour "islands" of dyskinetic mobility. Nevertheless the beneficial response to levodopa is rarely, if ever, lost at all. Complicated-parkinsonism patients, therefore, remain responsive to levodopa, and their postsynaptic DA receptors remain sensitive even during "off" periods.

Pharmacokinetic factors related to the long-term handling of levodopa may be relevant in the genesis of fluctuations. It is well demonstrated, in fact, that on-off phenomena can be controlled by keeping constant the levodopa blood levels. This fact, and the sensitivity of DA receptors, must be borne in mind in the treatment of complicated Parkinson's disease.

Intravenous Levodopa Infusion. In 1975 Shoulson first reported that by giving a continuous intravenous infusion of levodopa, together with oral carbidopa, it was possible to produce constant mobility and constant plasma drug levels in five fluctuating parkinsonian patients for periods of up to 4 hours. Subsequently, several authors confirmed the efficacy of levodopa infusion and demonstrated the availability of this therapeutic strategy even for longer periods of time. Hardie et al (1984) studied 14 patients with on-off fluctuations, comparing levodopa infusion with intravenous placebo. They definitely showed significant reduction in the number of daily on-off cycles, although some "off" periods were still present. Interestingly, Nutt et al. (1984), giving the infusion continuously for 20–36 hr, reported a striking worsening of dyskinesias and a loss of therapeutic benefits in some patients challenged with high-protein meals.

Marion et al. (1986) showed that by continuously adjusting the infusion rate in each patient, it is possible to maintain the clinical benefit of levodopa infusion for up to five consecutive days, giving a daytime infusion (12 hr) with drug-free nights. Following this procedure, we infused, for three consecutive days, 20 parkinsonian patients suffering from fluctuations in motor performance and dyskinesias. Levodopa (1 mg/ml; pH = 6.5) was given in association with oral carbidopa (75 mg/day) in a forearm vein. Seventeen patients turned "on" and remained mobile during all the infusion time, the levodopa rate range being 30–104 mg/hr (mean: 53.5 mg/hr). Three patients (of 20) showed akinetic periods lasting 30 to 120 min, always during the afternoon. These patients turned "on" again in the

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TABLE 1
Clinical Characteristics and Oral (OS) and Intravenous (IV) L-dopa Dosage, Twenty Patients

	Columbia		L-dopa os	L-dopa IV
Pt.	Off	On	mg/day	mg/day
SL	54	8	750	600
TF	57	10	750	600
SG	66	17	700	480
LL	69	13	800	480
DP	60	12	1000	600
ZD	63	22	500	540
FM	69	21	500	360
LP	50	11	1000	480
MI	67	8	1000	640
RL	59	17	750	600
FP	64	17	900	1200
DL	73	29	1000	720
SV	51	13	1250	720
FG	72	21	925	1200
RA	63	21	1000	660
AA	47	12	625	420
DC	61	26	810	720
DB	59	22	800	600
CA	47	15	500	600
PG	64	20	1000	720
Mean	53.1	13.05	828.0	642.0
SD	8.8	5.15	201.4	219.8

evening without modification of the infusion rate. Mild dyskinesias were still present during the "on" phases.

These studies clearly showed that the largest number of fluctuations in levodopa-treated Parkinson's disease are due to the oscillations in drug plasma levels. A lesser number of "off" periods seems not to be related to the pharmacokinetics of the drug and, in fact, they do not respond to levodopa intravenous infusion. Even if very effective, levodopa infusion cannot be used as a long-term treatment, but it is useful in post-surgical patients and as a predictive test for individual oral-levodopa need. In our study, in fact, there was a clear correlation between oral and intravenous drug dosage (Table 1).

The major limit on the use of levodopa infusion is its low solubility and high acidity. A highly water-soluble nonacid drug would therefore be a better practical choice for the infusion.

Intravenous Levodopa Methylester Infusion. The esterification of the carboxylic acid moiety of levodopa molecule gives a highly soluble and neutral prodrug. Levodopa methyl ester (ME) is highly soluble and, in animal studies, demonstrated to be equipotent with levodopa in reversing reserpine-induced akinesia in mice. The compound is split in vivo to levodopa and methanol.

Quinn gave levodopa ME (35 mg/ml) intravenously together with oral benserazide to three patients with severe PD, showing its efficacy at a mean rate of 269 mg/hr. No methanol was detected on the blood of two of these patients.

We infused levodopa ME (250 mg/ml; pH, 6.3) to three severely fluctuating parkinsonian patients for three consecutive days, comparing its clinical effect and blood levels to those obtained with standard intravenous levodopa. The clinical effects of the two drugs were similar. The patients remained mobile during each single infusion, and only one of them required an increase of dosage, late in the afternoon, with both drugs. The ME rate was three times higher (150 vs. 50 mg/hr) than the levodopa rate. The two drugs had similar pharmacokinetics but the area under the curve of ME was slightly larger. More evident was the increase of the area under the curve of 3-0-methyldopa detected during the ME infusions, when compared with the one obtained during standard levodopa infusions.

We gave ME subcutaneously to one patient but, despite the good clinical response, the infusion had to be stopped because of the local reaction, probably due to the high osmolarity of the solution.

Intravenous Lisuride Infusions. The studies with levodopa infusion demonstrated that by providing a constant and sufficient stimulation of the dopaminergic striatal system, it is possible to restore a good, prolonged mobility in almost all complicated-Parkinsonism patients. Efforts to use levodopa or its prodrug infusion as a long-term treatment failed.

Another useful compound for continuous intravenous infusion is the highly water-soluble ergot alkaloid lisuride, a potent DA agonist acting mainly on postsynaptic D_2 receptors. The cerebral bioavailability of lisuride seems to be free from competition in transport, and it is not affected by cerebral metabolites.

Obeso et al. in 1983 first reported a stable improvement in mobility in three parkinsonian patients giving a continuous infusion of 0.5–2 mg of lisuride over 8 hr (0.06–0.25 mg/hr). Their experience has now been extended to several other patients. In a majority of patients favorable results were obtained giving lisuride infusions in addition to usual oral treatment. All infusions were given with oral or intravenous domperidone. Quinn et al also tested lisuride infusions in a group of patients, demonstrating the good antiparkinsonian properties of the drug, but had the impression that "clearly lisuride infusion alone does not work in all patients."

We administrated an intravenous lisuride infusion to 20 parkinsonian patients, who had already been studied with levodopa infusion, during three consecutive days in a 12-hr study. Lisuride, 1 mg diluted in 500 mg of a saline solution, was infused in a forearm vein by a constant-volume pump. Initial infusion rate was 0.05 mg/hr; the rate was then adjusted as necessary on the following days to obtain an optimal clinical response. All patients received orally domperidone 60 mg/day to prevent systemic side effects. No other antiparkinsonian treatment was administered during the study. Lisuride dosage was increased until uncontrolled neurologic, psychiatric or systemic side effects were evident.

Seven (of 20) patients showed constant "on" periods during intravenous lisuride infusions, with an infusion rate ranging between 0.05 and 0.07 mg/hr (mean: 0.06 mg/hr). These patients were constantly mobile throughout each day of infusion. Mild dyskinesias were present in all but one patient in this group.

Seven (of 20) patients had a fluctuating response in which periods of dyskinetic mobility alternated with sudden switches to akinesia. The infusion rate in these patients ranged between 0.065 and 0.11 mg/hr (mean: 0.09 mg/hr). Further increase of dosage was ineffective and produced side effects (nausea, vomiting, dizziness).

Interestingly, all patients fully responding to lisuride reported that the "on" periods had a different quality than the "on" induced by intravenous treatment with L-dopa. Each patient indicated, in fact, a "less brilliant" mobility during lisuride "on" periods. Dyskinesias comparable to those seen on L-dopa were present during the "on" periods in all these patients.

Three patients showed improvement of symptoms (especially rigidity and tremor), but they did not swing to "on" with lisuride. In this group the drug infusion rate was between 0.15 and 0.20 mg/hr (mean: 0.18 mg/hr). Another three patients whose dosage was 0.08–0.15 mg/hr (mean: 0.11 mg/hr) were absolutely not responsive to lisuride because of severe systemic side effects (Table 2).

TABLE 2

L-dopa and Lisuride Intravenous Infusions, Twenty Patients

Pt.	L-dopa mg/12 hr	Lisuride μg/hr	Clinical effect	Columbia RS score OFF	Columbia RS score L-dopa IV	Columbia RS score Lisuride IV
SL	600	70	+ +	54	8	8
TF	600	60	+ +	57	10	10
SG	480	50	+ +	66	17	17
LL	480	50	+ +	69	13	13
DP	600	110	+ –	60	12	12
ZD	540	60	+ +	63	22	22
FM	360	65	+ –	69	21	21
LP	480	65	+ +	50	11	11
MI	640	50	+ +	67	8	8
RL	600	100	0	59	17	59
FP	1200	150	0	64	17	64
DL	720	200	–	73	29	49
SV	720	150	–	51	13	38
FG	1200	200	–	72	21	44
RA	660	140	+ –	63	21	21
AA	420	70	+ –	47	12	12
DC	720	70	+ –	61	26	26
DB	600	80	0	59	22	59
CA	600	70	+ –	47	15	15
PG	720	90	+ –	64	20	20
mean	642.00	100.0		60.75	16.75	26.45
SD	219.85	50.0		7.83	5.91	18.65

+ + = full responder; –: partial responder; + – = fluctuating; 0 = nonresponder.

Subcutaneous Lisuride Infusions. Because of the high solubility of the drug and the encouraging results obtained from the intravenous study, we gave lisuride subcutaneously to a group of 20 fluctuating Parkinsonian patients. The aim of the study was to evaluate the effect of long-term continuous dopaminergic stimulation. The study group consisted of 10 men and 10 women, aged 32–63 years (mean: 52.1 years), all with Parkinson's disease stage III to V (Hohen and Yahr). They had had symptoms of PD for 4–30 years (mean: 10.8 years) and had been taking levodopa 500–1250 mg/day (mean: 789.5 mg/day), together with a peripheral dopa decarboxylase inhibitor for 4–15 years. The criteria for selection were age under 65, incapacitating fluctuations in motor response while on oral levodopa, and no evidence of intellectual impairment or systemic diseases. "On-off" effects had been evident after an average of 6 years of levodopa treatment.

Lisuride 2 mg was diluted in 2 ml of sterile water and infused subcutaneously by insulin pump. The initial infusion rate was defined on the basis of previous intravenous lisuride infusions in the same patients and adjusted as necessary on the following days. Subcutaneous lisuride was given for 12 hr during the active day, and only if there was no satisfactory response was oral levodopa added. All patients received domperidone 60 mg/day to prevent systemic side effects.

After optimal infusion rates had been reached (range 0.55–0.80 mg/hr), 8 patients had constant and prolonged "on" period with lisuride. In this group the time spent in "off" decreased

TABLE 3
Lisuride Infusion, Single Treatment, Eight Patients
(mean values in parentheses)

	Columbia		Hours	Nocturnal	End-of-dose	
	On	Off	off/12 hr	akinesia	dystonia	Dyskinesia
Oral	13.0	51.2	3.8	2.6	1.7	2.1
	(5.1)	(11.4)	(0.8)	(0.7)	(1.3)	(1.1)
Infusion lisuride	12.6	48.0	0.5	1.2	1.1	1.3
	(4.4)	(10.7)	(0.5)	(0.4)	(0.8)	(1.0)

Mean dosage: 0.063 mg/hr.

from 3.8 hr (mean 0.8 hr) to 0.5 hr (mean 0.5 hr) (Table 3).

The remaining 12 patients needed small amounts of oral levodopa (100–875 mg/day) because lisuride alone at infusion rates of 0.5–0.11 mg/hr was not completely satisfactory. In this group the time spent in "off" decreased from 4.8 hr (mean 1.7 hr) to 0.7 hr (mean 0.5 hr). Statistical evaluation was based on 12-hr route only (Table 4).

Four patients in all, in fact, needed a 24-hr infusion to maintain nocturnal mobility. All patients complained of somnolence, nausea, and occasional vomiting during the first week of treatment; these effects gradually disappeared.

Twelve patients (of 20) are still under treatment, having been treated with lisuride infusions for 3–29 months. Seven of these are taking lisuride plus levodopa, and the remaining 5 are taking lisuride alone.

Eight patients dropped out of the study, three because of psychiatric side effects (2 of 3 were on 24 hr infusion), one because of vomiting; the remaining 4 patients withdrew for reasons not linked with therapy.

At the follow-up stage we think that lisuride administered by subcutaneous infusion is able to control fluctuations in motor performances in complicated PD, and that it could do so without levodopa.

Conclusions. Reviewing these data, it appears that continuous infusion is to date the therapeutic strategy able to give parkinsonian patients the longest and the most continuous periods of mobility. Even considering infusional compounds, levodopa is still the most effective antiparkinsonian drug in terms of number of responding patients and quality of clinical benefits. Unfortunately, neither levodopa or its prodrug levodopa methyl ester can be used as long-term infusional treatment. However, interesting results have been obtained using levodopa methyl ester in different oral formulations (data in press).

Lisuride is a potent dopaminergic drug but only in a small number of patients can it be administrated as a single treatment. However, when infused together with a small amount of levodopa, the majority of patients show impressive improvement of motor performance.

Recently, Stibe et al reported that Apomorphine infused subcutaneously is able to control fluctuations in motor performances when administrated in association with oral levodopa. In their experience Apomorphine produced fewer side effects than subcutaneous lisuride infusion.

TABLE 4
Associated Therapy, Eight Patients
(mean values in parentheses)

	Columbia		Hours	Nocturnal	End-of-dose	
	On	Off	Off/12 hr	akinesia	dystonia	Dyskinesia
Oral	18.2	54.8	4.8	3.0	1.1	1.7
	(6.1)	(11.5)	(1.7)	(0.7)	(0.8)	(0.7)
Infusion (lisuride + L-dopa)*	18.0	48.6	0.7	1.5	2.1	2.6
	(5.8)	(12.2)	(0.5)	(0.5)	(0.6)	(1.0)

* Mean dosages: lisuride 0.08 mg/hr + L-dopa 384 mg/day.

Even if such an approach makes it possible to control "on-off" fluctuations, the improvement of dyskinesia is poor, possibly due to the severe dysfunction of the receptor system, probably induced by long-term oral levodopa treatment.

We wonder whether providing continuous dopaminergic stimulation that begins in the earliest stages of the disease would avoid the development of "on-off" phenomena and dyskinesias.

Acknowledgments

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Extension of Life Span of Rats by Long-Term (-)Deprenyl Treatment

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As far as we now know, the nigrostriatal dopaminergic neuron is the most rapidly aging neuron in the brain. The dopamine content of the human caudate nucleus decreases by 13% per decade over age 45; dopamine itself is with high probability the culpable substance. The well-known main lines of metabolism of dopamine which inactivate the transmitter are the oxidative deamination and O-methylation catalyzed by MAO and COMT, respectively. For the age-related deterioration of the nigrostriatal dopaminergic neuron, however, metabolites originating from other catabolic pathways may—because of their cytotoxicity—be of prime importance.

A minor catabolic pathway for dopa leading to an indole derivative, dopachrom, was detected about 60 years ago. Among the intermediates leading to the indole derivatives, the ring-hydroxylated species, 6-OH-dopa and 6-OH-dopamine(6-OHDA), both generated in vivo, are the most potent neurotoxins. The autooxidation of 6-OH-dopa and 6-OH-DA leads to the genesis of the toxic free radicals, the superoxide (O_2^-) radical, the hydroxyl radical (OH ·), and to hydrogen peroxide (H_2O_2).

On the other hand, dopa and dopamine are oxidized to quinones, which readily react with nucleophiles within the neuron and bind irreversibly to proteins.

Thus the complex autooxidation of the high amounts of dopa and dopamine in the striatum, continuously generating substantial quantities of toxic free radicals and highly reactive quinones, creates a permanent danger for the nigrostriatal dopaminergic neuron, which has to mobilize its natural defensive measures to protect the neuron from the deleterious effect of the toxic byproducts of dopamine metabolism. It is now a general view that an age pigment is a biological marker of a free radical attack on the cell that inflicted damage but has resulted in successful expulsion of the attacker and sequestering of the damaged products (1).

Neuromelanin which is generated via the polyamerization of oxidative products of dopamine with the evident aim of finally depositing waste products is, in the human substantia nigra, the visible sign of the successful self-defense of the neuron against the free radicals and quinones originating from dopamine metabolism.

The sluggish depositing of neuromelanin in the human substantia nigra is in excellent agreement with this view. Graham (2) noticed that until a patient is at least 6 years old there is insufficient amount of neuromelanin in the substantia nigra to see it with an unaided eye. By cytophotometry, Mann et al (3) showed a linear increase in the pigmentation of the substantia nigra in humans from age 18 months to 60 years. Graham (4) calculated by morphometry that the volume of intraneuronal pigment increased linearly in direct relation to age. He found that the amount of pigment present in the eighth decade was twice that recorded in the fourth decade.

We may assume that the unavoidable, relatively slow, natural aging process of the nigrostriatal dopaminergic neuron is due to specific endogenous neurotoxins originating from dopamine, and Parkinson's disease may be a form of premature rapid aging of this system of unknown toxic origin. Be that as it may, it seems reasonable to develop drugs which provide protection against the self-produced neurotoxins and slow down the age-related changes in the nigrostriatal

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dopaminergic neuron, particularly because Parkinson's disease is still incurable and none of the therapeutic agents—including levodopa, now considered the best available therapy—stops its progression.

The aim of this study is to demonstrate that (-)deprenyl, which facilitates the activity of the nigrostriatal dopaminergic neuron in a unique manner and protects this neuron from the toxic effects of the highly selective neurotoxins 6-OHDA and MPTP, extends the lifetime of rats.

(-)Deprenyl Facilitates Activity of Nigrostriatal Dopaminergic Neuron

(-)Deprenyl, when administered continuously in small doses (0.25 mg/kg per day), facilitates the activity of the nigrostriatal dopaminergic neuron because of its highly characteristic complex spectrum of pharmacologic activity. According to my previous studies (5–14) selective inhibition of B-type MAO, inhibition of the uptake of dopamine, and facilitation of scavenger function are the mechanisms which may play the leading roles, whereas inhibition of the presynaptic dopamine receptors and accumulation of deprenyl metabolites in brain tissue, which releases dopamine from the neuron, play only subordinate roles, if they participate at all, in the genesis of deprenyl-induced increased dopaminergic tone in the striatum.

Deprenyl increases the firing rate of the nigrostriatal dopaminergic neuron. The striata of rats treated with 0.25 mg/kg deprenyl daily for three weeks emitted five times more dopamine in the resting state and seven times more dopamine in response to KCl stimulation than the striata removed from rats treated daily with 0.1 ml/100 g saline (10, 15). Deprenyl increases the rate of utilization of dopamine in the striatum. Whereas the striatum of untreated rats contained 52.7 ± 1.6 nmole/g dopamine and the turnover rate was found to be 13.7 ± 1.3 nmole/g per hour, the striatum of rats pretreated with 0.25 mg/kg (-)deprenyl daily for 28 days contained significantly higher amount of dopamine (81.77 ± 5.7 nmole) and the turnover rate increased significantly to 24.44 ± 1.1 (12, 16). The increase in the turnover rate of dopamine in the striatum was due to the enhancement of the fractional rate constant of dopamine efflux and the significant increase in the dopamine content.

The facilitation of striatal dopaminergic neurotransmission by long-term treatment is highly specific. A significant decrease in the turnover rate and unchanged level of noradrenaline in the brain stem was found (17), and no change in the turnover rate of serotonin treated daily with 0.25 mg/kg deprenyl for two weeks was detected (16).

The enhanced dopaminergic tone in the striatum of rats treated with deprenyl is further supported by our finding that the outflow of ACh from the cholinergic neurons of the caudate nucleus is significantly decreased in the striata removed from rats pretreated with 0.25 mg/kg deprenyl daily for two weeks.

In a series of experiments the acetylcholine content was found to be 0.69 nmole/mg protein in the striatum of untreated rats, whereas a significantly higher amount of acetylcholine (0.86 nmole/mg protein) was found in the rat striatum after two weeks pretreatment with (-)deprenyl; in the (-)deprenyl-treated group, the fractional rate constant of acetylcholine efflux from the cholinergic interneurons of the striatum decreased significantly, from 9.1 ± 0.8 to 6.2 ± 0.55 (12, 18).

We also measured the dynamics of the cholinergic function in the hippocampus. (-)Deprenyl treatment changed the turnover of ACh in the caudate nucleus via the activation of the nigrostriatal dopaminergic neuron without having any direct influence on cholinergic transmission. This was proved by our finding that the dynamics of cholinergic function in the hippocampus of (-)deprenyl-treated rats remained unchanged (18).

With regard to the mechanism of facilitation, the complexity of the pharmacological profile of (-)deprenyl needs consideration. Interestingly, a single injection of 0.25 mg/kg (-)deprenyl, which is sufficient to block B-type MAO activity in the brain, has no remarkable effect on the activity of the nigrostriatal dopaminergic neuron. Daily administration of 0.25 mg/kg deprenyl for two to four weeks is needed to demonstrate the peculiar deprenyl-induced changes in the activity of the striatal dopaminergic system. We were unable to stimulate the deprenyl-induced changes in the central nervous system with either long-term administration of pargyline, a semiselective MAO-B inhibitor, or such close structural relatives of deprenyl as TZ-650, U-1424 (19), although these structural relatives proved to be as selective as deprenyl in inhibiting B-type MAO. This observation substantially supports our view that deprenyl facilitates the activity of the nigrostriatal dopaminergic neuron because of its unique pharmacologic profile, created by the interplay of a series of mechanisms of action of which the ability to block MAO-B selectively is only one important component.

MAO-B Activity. Deprenyl was the first compound identified as blocking B-type MAO selectively (20) and is still the internationally accepted reference substance for inhibiting MAO-B selectively in different animal species and in humans. (-)Deprenyl is a highly potent and safe inhibitor of B-type MAO. We were able to block MAO-B activity in the brain selectively in vivo in four species (mouse, rat, cat, dog) with subcutaneous administration of 0.17%–0.31% of LD_{50} (6). In the rats the highest dose of deprenyl which blocked MAO-B activity, leaving MAO-A activity functionally unaffected, was 0.25–0.5 mg/kg. In higher doses, deprenyl begins to block MAO-A activity considerably. We also demonstrated that daily administration of 0.25 mg/kg deprenyl for 21 days does not change the selectivity of MAO-B inhibition (21).

Uptake of Dopamine in Striatum. (-)Deprenyl inhibits the uptake of monoamines into the nerve endings of catecholaminergic neurons, and the effect is independent of the MAO-inhibiting property of the compound.

(-)Deprenyl is an inhibitor of the uptake of dopamine in the striatum in vivo. One hour after a single injection of 0.25 mg/kg (-)deprenyl, the uptake of dopamine in the striatum decreased significantly (from 474 ± 31 pmol/mg protein per 5 min to 364 ± 29 pmol/mg protein per 5 min), but no change in the uptake of dopamine could be detected 24 hours after the single injection. If (-)deprenyl was given daily for two weeks and the last injection of the drug was given 1 hour prior to the removal of the striatum, a higher degree of inhibition of dopamine uptake (from 420 to 284) was measured. In the rats treated with (-)deprenyl daily for two weeks, the uptake of dopamine remained significantly lower (decreased from 462 to 359) even in the striatum removed 24 hours after the last injection of (-)deprenyl (14).

Uptake of Tyramine in Noradrenergic Nerve Terminals. Tyramine played a special role in the history of the MAO inhibitors. It is well known that the "cheese effect" is the most serious side reaction of the MAO inhibitors in clinical use. Potentiation of the pressor effect of tyramine is likely to be the main cause of dangerous hypertensive reactions which supervene after the intake of certain food materials containing high amounts of free amine (cheeses, yeast products, beans, Chianti vines, pickled herring, chicken liver) in patients treated with MAO inhibitors. This "cheese reaction" seriously discredited the MAO inhibitors and restricted their therapeutic use, which requires careful medical control. It is now the general view that the potential toxic effects of the inhibitors are greater and more serious than those of any other group of psychotherapeutic agents. The "cheese effect," first described by Blackwell (22), is thought to be primarily a consequence of inhibition of the intestinal enzyme.

(-)Deprenyl does not have this adverse effect for two reasons: it inhibits the uptake of tyramine; and when administered within the therapeutic dose range as a selective inhibitor of MAO-B it leaves the MAO activity of the intestine practically unchanged (9).

That deprenyl is a potent inhibitor of the noradrenaline-releasing effect of tyramine in smooth muscle in vivo and in vitro was first demonstrated by Knoll et al. in 1967 (23) and studied in detail in a number of papers (5, 6, 20, 24–26). (-)Deprenyl proved to be highly efficient in blocking the uptake of tyramine into the noradrenergic nerve terminals in tests of various isolated smooth muscle, including nictitating membrane of the cat, central ear artery and main pulmonary artery strip of the rabbit, rat vas deferens.

We introduced the pulmonary artery strip of the rabbit as an experimental model for testing and comparing the tyramine-potentiating effect of MAO-B inhibitors on vascular smooth muscle. This test allows prediction of the safety of these inhibitors in humans. We found in the test that, as expected, the nonselective MAO inhibitors (tranylcypromine, phenelzine, isocarboxazid, nialamid), as well as the A-selective MAO inhibitors (clorgyline and Lilly 51641) are highly potent in potentiating the effect of tyramine. However, the B-selective MAO inhibitors had the same potency (14, 27). Deprenyl, on the one hand a potent and selective inhibitor of B-type MAO and on the other also an efficient inhibitor of noradrenaline release induced by indirectly acting monoamines, is at present the only safe MAO inhibitor for long-term treatment.

Protection from the Neurotoxicity of 6-OHDA. The physiologic consequences of dopaminergic regulation in the caudate nucleus are detectable by measuring the basal and ouabain-stimulated release of ACh in the striatum of the rat, as I have shown in prior papers (6, 9, 12, 14). There is a substantial increase in the rate of acetylcholine released from isolated striatal slices dissected from 6-OHDA pretreated rats.

In a new series of experiments we found that the striata of untreated rats emitted 404.2 ± 36.2 pmole/g per min acetylcholine to ouabain stimulation, but the striata dissected from rats pretreated with 6-OHDA released 811.4 ± 49.2 pmol/g per min ($p < 0.001$). This is clear-cut evidence that the nigrostriatal dopaminergic neurons play a rate-limiting role in controlling the release of acetylcholine in the caudate nucleus.

(-)Deprenyl completely prevented the effect of 6-OHDA in a group of rats pretreated with 0.25 mg/kg (-)deprenyl for 21 days prior to 6-OHDA treatment; 451.8 ± 51.3 pmole/g per min acetylcholine was released to stimulation from the striata.

The degeneration of the dopaminergic neurons leads to postsynaptic dopamine receptor supersensitivity. We therefore studied the effect of repeated injections of (-)deprenyl on the dopamine receptor binding in 6-OHDA treated rats (16). We found the specific binding of ^{3}H-propylnorapomorphine in striatum membrane of rats to be 169.7 ± 7.0 fmole/mg protein. After 6-OHDA treatment the specific binding of the ligand increased significantly to 197.9 ± 10.9 fmole/mg protein, indicating postsynaptic dopamine receptor supersensitivity resulting from 6-OHDA-induced degeneration of the nigrostriatal dopaminergic neuron. The binding of the ligand, however, remained unaltered (169.9 ± 6.4 pmole/mg protein) in rats pretreated with 0.25 mg/kg deprenyl for 3 weeks prior to 6-OHDA administration; that is, daily subcutaneous administration of 0.25 mg/kg (-)deprenyl completely abolished the receptor supersensitivity resulting from 6-OHDA pretreatment. Because (-)deprenyl by itself does not displace dopamine receptor ligand binding in low concentration, these data furnish further evidence for the conclusion that (-)deprenyl protects the nigrostriatal neuron from the neurotoxic effects of 6-OHDA.

As for the mechanism of action of this protection, blockade of B-type MAO, inhibition of the uptake of 6-OHDA into the neuron and the facilitation of scavenger function, and improved removal of the neurotoxic free radicals may share in the highly efficient shielding effect of (-)deprenyl.

Protection from the Neurotoxicity of MPTP. A new experimental model for studying Parkinson's disease is the specific neurotoxin 1-methyl-4-phenyl-1,2,5,6-tetra-hydropyridine (MPTP), which was found to induce severe parkinsonian symptoms within a short time in monkeys and humans. MPTP is oxidized by B-type MAO and the toxic intermediate(s) generated during the oxidation process kill(s) the nigrostriatal dopaminergic neuron.

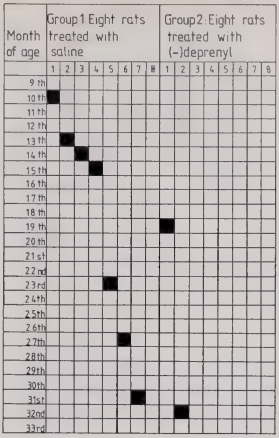
Cohen et al (28) demonstrated that (-)deprenyl also prevents the neurotoxic effect of MPTP on the nigrostriatal dopaminergic neuron in a strain of monkeys, Macaca fascicularis. In these monkeys 0.35 mg free base/kg MPTP was injected intravenously on four successive days; at 11–12 days after the last dose, the dopamine and homovanillic acid (HVA) content in the head of the caudate and the ^{3}H dopamine uptake into synaptosomes of the tissue was measured. Whereas the control caudate contained 11.4 ± 1.0 μg/g dopamine and 9.1 ± 0.7 μg/g HVA, and 0.53 ± 0.14 pmol/mg ^{3}H dopamine was taken up into the synaptosomes, in MPTP-treated monkeys the dopamine and HVA content was practically nil and there was no sign of DA uptake into synaptosomes. Those monkeys, however, which were injected i.m. with priming doses of 10 mg free base/kg (-)deprenyl for 4 days, followed by daily maintenance doses of 2 mg/kg to the end of the experiment, and MPTP injected at 2 h after (-)deprenyl starting with the 4th priming dose, were protected against the neurotoxic effect of MPTP.

Both the dopamine content of the caudate (11.4 ± 1.4 μg/g) and the dopamine uptake into the synaptosomes prepared from the tissue (0.53 ± 0.13 pmol/mg tissue) remained completely unchanged.

Hypothesis: Long-Term (-)Deprenyl Treatment Counters Age-Related Decay of Nigrostriatal Dopaminergic Neuron

Aging, the decline of the quality of life with the passage of time, is the unfortunate common fate of all living beings, but this common fate does not mean that nothing can be done to improve the quality of life in senescence. We can seek such an improvement by starting to prevent or at least to slow down the aging processes as early as possible in the life of mature adults. No single age has been pinpointed as the start of sharp decline of a function. Each individual has his or her own level of performance and kind of dissociation between chronological and physiologic age. Commonly, the performance on one test of an 80-year-old healthy person may equal the average performance of 40-year-olds, whereas on another test the same person's performance equals the age-cohort results, and in a third test falls much below the age-cohort average.

Age-related changes that will eventually diminish the quality of life begin to develop in younger mature adults. The only reasonable strategy for improving the quality of life in senes-



Month of age	Group 1 Eight rats treated with saline								Group 2: Eight rats treated with (-)deprenyl							
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
9th																
10th	■															
11th																
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Fig. 1. Survival of sluggish male CFY rats treated from age 8 months with saline (0.1 ml/100 g per day, subcutaneous) or (-)deprenyl (0.25 mg/kg per day, subcutaneous). ■ died.

cence is therefore to detect the most important of the slowly developing biochemical lesions of aging, to understand the nature of these lesions one by one, and to take arms against the physiologically unavoidable changes in due time. If we clearly understand the molecular mechanism of a biochemical lesion of aging, we have a much better chance of developing an appropriate drug strategy for slowing down the development of this lesion and countering its consequences.

The search for such new lines of medication of the elderly might be based on the assumption that the decline of the functional capacity of the aging organism is due to the development of age-related biochemical lesions, the consequences of which can be counteracted by appropriate continuous medication (8).

As an example, I have proposed the possibility of slowing down the age-related decrease of striatal dopamine by continuous administration of (-)deprenyl (7, 8, 10, 13).

In 1957 Montagu detected the presence of dopamine in the central nervous system (29) and Bertler and Rosengren reported in 1959 that about 80% of dopamine in the human brain is localized in the basal ganglia (29a). An age-dependent decrease in the dopamine content of the basal ganglia in humans was soon detected by Bertler (30) and corroborated by many others. The change in brain dopamine is not only statistically but also biologically highly significant. The age-related progressive decline of dopaminergic control in the brain seems now to be the first firmly established biochemical lesion of aging.

Year by year we learn more about the biochemical and morphological changes within the aging brain which seem to compose the intertwining chains of a vicious circle resulting in the irresistible decline of the dopaminergic tone in senescence.

Decrease in Tyrosine Activity. McGeer et al reported in 1971 (31) that the activity of tyrosine hydroxylase, the enzyme catalysing the rate-limiting step in catecholamine biosynthesis, decreases tremendously in human brain tissue with increasing age.

Increase in MAO-B Activity. In the same year, Robinson et al (32) demonstrated that MAO activity progressively increases in the aging brain, securing more favorable conditions for the catabolism of brain dopamine in senescence. The age-dependent change in MAO activity was studied in detail in a number of papers, leading to the unequivocal conclusion that B-type MAO activity increases selectively with advanced age in both the human and the rat brain, and that the age-dependent increase in MAO-B activity is due entirely to higher enzyme concentration in brain tissue.

In looking for an explanation for the age-related selective increase of MAO-B activity, one has to consider that in both animals and humans MAO-B is predominantly localized in the neuroglia. Cell loss is a general feature of the aging brain. A more or less constant pattern of loss of cortical neurons, up to 30% of the total neuronal pool, was found in the human brain with increasing age. A drop of the number of neurons from 7890/nm^3 at age 45 to 5800/nm^3 at age 90, a loss of 26%, was found in the hippocampal cortex, using a highly sophisticated counting arrangement (33). Because the loss of neurons is always compensated for by glial cells, the progressive and cumulative loss of neurons in the aging brain gives a satisfactory explanation to the selective increase of extrasynaptosomal MAO-B activity with increasing age.

Functional Consequences. As for the functional consequences of such a change in the brain, we have to consider the possible physiological significance of extraneuronally localized MAO-B for interneuronal communication in the central nervous system. Let us take dopamine, a substrate of MAO-B, as an example.

Dopamine may transmit a message from one neuron to another in one of two ways. The dopaminergic nerve terminal may be in synaptic con-

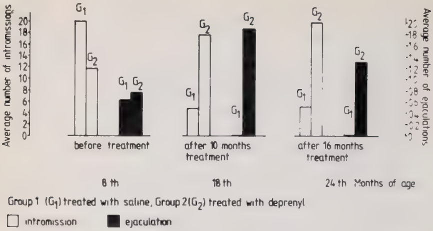

Fig. 2. Sexual performance of sluggish male CFY rats before and after long-term treatment with saline (0.1 ml/100 g per day, subcutaneous) and deprenyl (0.25 mg/kg per day, subcutaneous). Sexual activity was tested once a week as described by Dallo et al 1986 (37).

tact with the target neuron. In this case the released dopamine molecules immediately reach the target cell and are rapidly eliminated by reuptake.

On the other hand—and possibly the usual case—dopamine is released from the nerve terminals and there is no synaptic contact. (Note that the relative paucity or even lack of synaptic junctions seems now to be a common feature to central monoamine axon terminals). Morphologic evidence for this second path with regard to the neostriatum was shown by Hokfelt (34) and Tennyson et al (35). Such a morphologic situation means, however, that the dopamine molecules have to scatter and travel a considerable distance to reach the target cell. Whereas in the case of synaptic contact between the neurons, the extraneuronal MAO-B activity is evidently unable to influence the effectiveness of the chemical message delivered by dopamine, in the case of a nonsynaptic interneuronal communication the situation is essentially different. In this case the chances of the slowly diffusing molecules reaching their target cell and modulating its activity might essentially depend on the concentration of the glial MAO-B in the environment.

Collating the fact of an unavoidable loss of neurons with the inescapable result of increased MAO-B activity with increasing age makes it understandable that dopaminergic modulation in the brain is progressively decreasing in the aging brain.

As for the consequences of this biochemical lesion of aging, I have advanced the concept that the age-related decrease of dopaminergic tone in the brain plays a role in the high incidence of adverse changes in affective behavior, sexual performance, and motor coordination in advanced age (7, 8).

Rat Sexual Performance and Deprenyl. I, with colleagues, selected sexual performance of male rats as an experimental model to check the validity of the hypothesis that long-term administration of (-)deprenyl may improve a dopamine-dependent function which deteriorated in an age-dependent manner. Selection of this model was supported by the experience that sexual performance of male rats is a quantifiable dopamine-dependent function decreasing with age. Using this model (36) we were able to demonstrate that the continuous administration of low doses of (-)deprenyl increased the sexual vigor of aged male rats significantly.

Rat Life Span and Deprenyl. In a new series of experiments we decided to analyze the effect of long-term administration of small daily doses of (-)deprenyl on the life span of male rats. The longevity study started in 1985 and is still unfinished.

We selected male CFY rats which proved to be sexually sluggish. The rats were kept under standard conditions. Methodologic details of selection and testing were as described in Knoll et al (36) and Dallo et al (37). Selection was based on sexual performance of the rats tested once a week for four consecutive weeks, starting at age eight months. Males which did not produce more than one ejaculation during the four consecutive tests but displayed intromissions were selected as sexually sluggish males.

For the first series of experiments, 16 males were selected and were divided into two groups of eight. Experimental treatment started at age nine months. Group 1 (G_1) was treated with saline (0.1 ml/100 g per day, subcutaneous), Group 2 (G_2) with deprenyl (0.25 mg/kg per day, subcutaneous). Sexual performance was tested once a week.

The survival rate of the rats in the two groups until age 33 months was conspicuously different (Fig. 1). Up to the end of the 33rd month, 7 rats in G_1 died, whereas only two rats in G_2 died. This seems to show that long-lasting treatment with deprenyl extends the life span of rats. Observation of the survivors continues.

The sexual performance of the two groups 10 and 16 months after continuous treatment (Fig. 2) is in excellent agreement with our earlier findings; the sexual performance of the deprenyl-treated group is much better than that of the saline-treated group.

Experimental Data and Clinical Experiences. (-)Deprenyl, still the only MAO inhibitor that can be safely combined with levodopa, was introduced as a new therapeutic agent in Parkinson's disease in 1975 by Birkmayer et al. Its place in the therapy of Parkinson's disease is now firmly established (38).

In a series of 1987 papers the beneficial effect of (-)deprenyl treatment in Alzheimer's disease was demonstrated (39–41). The nigrostriatal dopaminergic neuron, which contains mainly MAO-B in humans, belongs to one of the most important catecholaminergic stimulatory systems in the brain. The usefulness of (-)deprenyl in Alzheimer's disease might well be the consequence of the activation of the nigrostriatal dopaminergic neuron which stimulates mental functions in a nonspecific manner. In rat experiments, for example, inducing one-sided lesions of the substantia nigra leads to grave learning deficits (42).

(-)Deprenyl is a clinically active antidepressant. This was first demonstrated by Varga and Tringer for the racemic form (43) and for (-)deprenyl by Tringer et al (44). The first clinical trials using the selective dose range of (-)deprenyl were performed by Mann and Gershon (45, 46), who also found the substance to be an effective antidepressant.

In animal experiments (-)deprenyl exerted a number of effects described to be characteristic for antidepressants. Daily injections of (-)deprenyl in the MAO-B selective dose range (1 μmole/kg, subcutaneous) attenuated noradrenaline-dependent stimulation of cortical adenylate cyclase and reduced the number of brain recognition sites for β-adrenergic receptor ligands. Such an effect is typically elicited by antidepressants and is not at all specific to (-)deprenyl; the semiselective MAO-B inhibitor pargyline (2.5 μmole/kg per day for 3 weeks) acted similarly. (-)Deprenyl, however, exerted a unique effect not produced by pargyline: it increased the number of (^{3}H) imipramine recognition sites (47), an effect recently described in mice as well (48). The physiologic relevance of the increase remains obscure. Further studies must explore and find a possible clinical relevance of this peculiar effect following the repeated administration of small doses of (-)deprenyl.

What we feel to be of great importance for the future is the harmony of our longevity study and the finding that the addition of (-)deprenyl to Madopar prolonged the life span of parkinsonian patients (49, 50), suggesting the retardation of the degeneration of dopaminergic neurons. So far no other antiparkinsonism drug is known to have this property.

Putting experimental data and theoretical considerations together, it seems likely that those unavoidable age-related morphologic and biochemical changes which lead to a progressive decline of dopaminergic activity in the elderly have serious functional consequences. The door is now open for medical science to devise an appropriate long-term treatment strategy aimed at preventing or at least partially countering the problems caused by dopamine deficiency in the aging brain.

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Effects of Dietary Amino Acids, Carbohydrates, and Choline on Neurotransmitter Synthesis

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The perception that eating foods rich in proteins can, in some parkinsonian patients, diminish the clinical efficacy of L-dopa (1, 2) has drawn the attention of neurologists to a broader phenomenon, the fact that brain composition and function are influenced to a remarkable extent by plasma levels of various nutrients, and thus at least potentially by what one has eaten (3, 4).

Foods or nutrients cause characteristic modifications in the composition of the plasma, particularly in plasma levels of most of the large neutral amino acids (LNAA) (5, 6) and of choline (7). These cause parallel changes in brain amino acid (8, 9) and choline (10) levels, which, in turn, affect the rates at which particular neurons convert tryptophan (11), tyrosine (12), and choline (10, 13) to serotonin, the catecholamines, and acetylcholine, respectively (3, 10, 14).

This ability of a meal to increase or decrease brain neurotransmitter synthesis continues to seem very strange: It lacks known counterparts in endocrinology, where eating foods rich in cholesterol does not increase the production of testosterone or estradiol, and eating fish does not enhance thyroxine production unless one happens to be hypothyroid. One cannot but wonder about how it might be advantageous to the body to couple the outputs of certain neurons to food-induced changes in plasma composition, and how disturbances in this coupling might contribute to neurologic or behavioral disorders. The nutrient dependence of some neurons also provides physicians with a novel strategy—based on using supplemental nutrients as though they were drugs—for attempting to treat disorders that involve these neurons.

Dietary Carbohydrates and Proteins and Brain Serotonin

The initial observation that food consumption can affect neurotransmitter synthesis was made in studies on rats performed in 1971 (11). Animals were allowed to eat a test diet that contained carbohydrates and fat but lacked protein. Soon after the start of the meal, brain levels of the essential (and scarce) amino acid tryptophan were found to have risen, thus increasing the substrate-saturation of the enzyme, tryptophan hydroxylase, which controls serotonin synthesis. The resulting increase in brain serotonin levels was associated with an increase in brain levels of serotonin's chief metabolite, 5-hydroxyindole acetic acid (5-HIAA), suggesting that serotonin release had also been enhanced.

The rise in brain tryptophan levels that occurred after the consumption of a carbohydrate-rich meal was accompanied, in rats but not humans, by a small increase in plasma tryptophan levels. Both of these changes had been unanticipated, since the insulin secretion elicited by dietary carbohydrates was known to lower plasma levels of most of the other amino acids.

However, plasma tryptophan's unusual re-

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sponse to insulin was recognized, soon thereafter (15), as resulting from another unusual property of the amino acid, its propensity to bind loosely to circulating albumin: Insulin causes nonesterified fatty acid (NEFA) molecules to dissociate themselves from albumin and to enter adipocytes. This dissociation increases the protein's capacity to bind circulating tryptophan; hence, whatever reduction insulin causes in "free" plasma tryptophan levels is compensated for by a rise in the albumin-bound moiety, yielding, in humans, no net change in total plasma tryptophan levels. (Since this binding is of low affinity, the albumin-bound tryptophan is almost as able as "free" tryptophan to be taken up into the brain [16].)

Much more difficult to explain were the data obtained subsequently on what happened to brain tryptophan and serotonin levels after rats consumed a meal rich in protein: Although plasma tryptophan levels rose, reflecting the contribution of some of the tryptophan molecules in the protein, brain tryptophan and serotonin levels either failed to rise or, if the meal contained a high proportion of protein, actually fell (8).

The explanation for this paradox was found to lie in the kinetic properties of the transport systems that carry tryptophan across the blood-brain barrier (17) and into neurons (18, 19): The endothelial cells which line central nervous system capillaries contain various macromolecules which shuttle specific nutrients or their metabolites between the blood and the brain's extracellular space (17). One such macromolecule mediates the transcapillary flux (by facilitated diffusion) of tryptophan and other LNAA; others move choline, basic or acidic amino acids, hexoses, monocarboxylic acids, adenosine, adenine, and various vitamins. The macromolecule transporting the LNAA attaches its ligands competitively with each other.

Hence the ability of circulating tryptophan molecules to enter the brain is increased when plasma levels of the other LNAA fall (as occurs after insulin is secreted [20]), and diminished when the other LNAA rise. Since all dietary proteins are considerably richer in the other LNAA than in tryptophan (only 1.0%–1.5% of most proteins), consumption of a protein-rich meal decreases the "plasma tryptophan ratio" (the ratio of the plasma tryptophan concentration to the summed concentrations of its major circulating competitors for brain uptake: tyrosine; phenylalanine; the branched-chain amino acids leucine, isoleucine, and valine; methionine). This, in turn, decreases tryptophan's transport into the brain and slows its conversion to serotonin. (Similar competitive mechanisms also mediate the fluxes of tryptophan and other LNAA between the brain's extracellular space and its neurons; moreover, similar plasma ratios predict brain levels of each of the other LNAA after treatments that modify plasma amino acid patterns.)

It seems counterintuitive that the meal which most effectively raises brain tryptophan levels is the one that lacks tryptophan entirely (that is, one containing carbohydrates but no proteins), while a protein-rich meal, which elevates blood tryptophan concentrations substantially, has the opposite effect on the brain. Plasma tryptophan ratios in normal individuals vary between about 0.065 and 0.160 (5, 6), depending largely on the composition of the last meal (or snack) eaten, and the interval that has passed since its ingestion. In rats such variations are capable of causing sizable differences in brain tryptophan levels. Subnormal plasma tryptophan ratios are often noted in obese people, reflecting elevated plasma levels of the branched-chain amino acids (21), perhaps caused by insulin resistance; these ratios are further reduced if the subjects are put on a high-protein, low-carbohydrate diet.

The fact that giving pure tryptophan can increase brain serotonin synthesis, and can thereby affect various serotonin-dependent brain functions (sleepiness; mood) had been known at least since 1968. What was novel and perhaps surprising about the above experiments was their demonstration that brain tryptophan levels—and serotonin synthesis—normally undergo important variations in response, for example, to the decision to eat a carbohydrate-rich vs. a protein-rich breakfast.

It remained possible, however, that mechanisms might exist outside the serotonin-releasing neuron itself, which kept precursor-induced increases in the transmitter's synthesis from causing parallel changes in the amounts that actually were released into the synapses. Indeed, it was known that if rats were given very large doses of tryptophan—sufficient to raise brain tryptophan levels well beyond their normal range—the firing frequencies of their serotonin-releasing raphe neurons decreased markedly; this was interpreted as reflecting the operation of a feedback system designed to keep serotonin release within a physiologic range. (Similar decreases in raphe firing had also been observed in animals given drugs, like MAO inhibitors or serotonin-reuptake blockers, which cause persistent increases in intrasynaptic serotonin levels.) However, if rats were given small doses of tryptophan—sufficient to raise brain tryptophan levels, but not beyond normal peaks—or if they consumed a carbohydrate-rich meal, which raised brain tryptophan levels physiologically, no decreases in raphe firing occurred.

Hence, food-induced changes in serotonin synthesis are able to affect the amounts of serotonin released per firing without slowing the neuron's firing frequencies, and thus are "allowed" to modulate the net output of information from serotoninergic neurons. (This output is, theoretically, the product of three factors: the number of serotonin-releasing nerve terminals; the average frequency with which the raphe neurons happen to be firing; and the average number of serotonin molecules released at each terminal per firing.) The physiologic range of serotonin release per unit time apparently is broad.

Tryptophan, Dietary Carbohydrates, and the Human Brain

The ability of supplemental tryptophan to enhance serotonin turnover within the human central nervous system (for example, to elevate CSF 5-HIAA levels) was first shown in 1970 (22); apparently, no neurochemical data are available on the human brain's responses to carbohydrate intake. Numerous behavioral and neurologic effects have been associated with tryptophan administration, starting with Smith and Prockop's original observation that it caused drowsiness and euphoria (23). Most of these effects have been reviewed extensively elsewhere (24–28) and are not further discussed here. In experimental animals, tryptophan is antihypertensive and enhances the release of growth hormone; its effects on plasma prolactin levels in humans, and on corticosterone levels in the rat, remain uncertain.

Only a few well-controlled studies have been published describing behavioral effects of dietary carbohydrates (28). Some of these have involved administering a specific carbohydrate, sugar (sucrose), to hyperactive children whose parents or teachers believed that this carbohydrate exacerbated their behavioral problem. In general, consumption of the sugar tended, if anything, to reduce activity, similar to its (and tryptophan's) reported effect on normal individuals: a high-carbohydrate lunch increased sleepiness in women, calmness in men, and, in subjects over forty, the tendency to commit errors in a standardized test of performance (29).

Apparently, hyperactive children consume larger quantities of sugar than control subjects (30), if they are allowed the opportunity to do so. This could reflect a greater need for energy, or, conceivably, an unrecognized attempt at self-medication, similar to that postulated below for patients with the seasonal affective disorder syndrome (SADS) and for other groups of carbohydrate cravers (31): Perhaps the raphe neurons of such patients release "inadequate" quantities of serotonin, causing them to feel dysphoric; consumption of carbohydrates might then be expected to ameliorate these feelings, if only temporarily, by augmenting serotonin release. There is evidence that levels of serotonin or 5-HIAA are subnormal in CSF samples from violent psychiatric patients (24) and in brains of people who have died by suicide (26, 27), but apparently there is no information about serotonin levels or turnover in brains of hyperactive children.

Brain Serotonin, Nutrient Choice, and Carbohydrate Craving

If rats are allowed to pick from foods in two pans, presented concurrently, which contain differing proportions of protein and carbohydrate, they choose among the two so as to obtain fairly constant (for each animal) amounts of the macronutrients (32). However, if prior to "dinner" they receive either a carbohydrate-based "snack" (33) or a drug that facilitates serotoninergic neurotransmission (32), they quickly modify their food choice, selectively diminishing their intake of carbohydrates.

These observations support the hypothesis that the responses of serotoninergic neurons to food-induced changes in the relative concentrations of plasma amino acids allow these neurons to serve a special function, as "sensors," in the brain's mechanisms governing nutrient choice (31): Perhaps they participate in a feedback loop through which the composition of "breakfast" (that is, its proportions of protein and carbohydrate) can—by increasing or decreasing brain serotonin levels—influence the choice of "lunch."

A similar mechanism may operate in humans: Subjects housed in a research hospital were allowed to choose from six different isocaloric foods (containing varying proportions of protein and carbohydrate, but constant amounts of fat) at each meal, taking as many small portions as they liked; they also had continuous access to a computer-driven vending machine, stocked with mixed carbohydrate-rich and protein-rich isocaloric snacks. It was observed (34, 35) that the basic parameters of each person's food intake —total number of calories; grams of carbohydrate and protein; number and composition of snacks—tended to vary within only a narrow range, day to day, and to be unaffected by placebo administration.

To assess the involvement of brain serotonin in maintaining this constancy of nutrient intake, pharmacologic studies were undertaken in individuals in whom the putative feedback mechanism might be impaired. These were obese people who claimed to suffer from "carbohydrate craving," manifested as their tendency to consume large quantities of carbohydrate-rich snacks, usually at a characteristic time of day or evening (35).

Subjects were given D-fenfluramine (Isomerid), a drug which had been found (32) to decrease carbohydrate intake in normal rats, and to cause weight loss in obese people by a mechanism involving the release of brain serotonin. Administration of relatively low doses (15 mg, twice daily), caused a major reduction in snack carbohydrate intake (34, 35); a smaller reduction in mealtime carbohydrates (35); and no significant changes in mealtime protein (35) or fat intake. (Too few protein-rich snacks were consumed by the subjects to allow assessment of the drug's effect on this source of calories.)

Other drugs also thought to enhance serotonin-mediated neurotransmission selectively, for example the antidepressants zymelidine, fluvoxamine and fluoxetine, also have been found to cause weight loss; this contrasts with the weight gain (and carbohydrate craving) often associated with less chemically specific antidepressants like amitriptyline. It has not yet been determined whether these drugs also selectively suppress carbohydrate intake in humans.

Serotonin: Link between Appetitive and Affective Symptoms? Severe carbohydrate craving is also characteristic of patients suffering from SADS, a variant of bipolar clinical depression associated with a Fall onset; a higher frequency in populations living far from the equator; and concurrent hypersomnia and weight gain (36, 37). A reciprocal tendency of many obese people to suffer from affective disorders (usually depression) has also been noted (37). Since serotoninergic neurons apparently are involved in the actions of both appetite-reducing and antidepressant drugs, they might constitute the link between a patient's appetitive and affective symptoms: Some patients with disturbed serotoninergic neurotransmission might consult their physicians for obesity, reflecting their overuse of dietary carbohydrates to treat their dysphoria. (The carbohydrates, by increasing intrasynaptic serotonin, would mimic the neurochemical actions of bona fide antidepressant drugs like the MAO inhibitors and tricyclic compounds.) Other patients might bring to their physician a complaint of depression, and their carbohydrate craving and weight gain would be perceived as secondary problems. Another group of patients—the nonanorexic bulimics—might seek medical assistance because of their concurrent food binges and depression or anxiety. Yet another group might include women with the premenstrual syndrome, with late luteal phase mood disturbances, weight gain, carbohydrate craving, and sometimes fluid retention. The participation of serotoninergic neurons in a large number of brain functions besides nutrient-choice regulation might have the effect of making such functions hostages to eating (seen in the sleepiness that can, for example, follow carbohydrate intake [29]), just as it could cause mood-disturbed individuals to consume large amounts of carbohydrates for reasons related neither to the nutritional value nor taste of these foods. In support of this view, we have recently found D-fenfluramine to be an effective treatment for both the affective and the appetitive symptoms of SADS (38).

Under What Circumstances Will Nutrient Intake Affect Neurotransmission?

On the basis of the tryptophan-serotonin relationship, one can formulate a sequence (3) of biochemical processes that would have to occur for any nutrient to affect the synthesis of its neurotransmitter product, and the additional steps that would be required for the nutrient also to affect the release of the neurotransmitter:

A. Plasma levels of the precursor (and of other circulating compounds, like the LNAA for tryptophan that affect its availability to the brain) must be "allowed" to increase after its administration (or after its consumption as a constituent of foods). That is, plasma levels of tryptophan or the other LNAA, or of choline, cannot be under tight homeostatic control (like, for example, plasma calcium or osmolarity). In actuality, plasma levels of tryptophan, tyrosine, and choline do vary severalfold after the consumption of normal foods, and those of the branched-chain amino acids may vary as much as fivefold or sixfold.

B. The brain level of the precursor must be dependent upon its plasma level, that is, there must not be an absolute blood-brain barrier for circulating tryptophan, tyrosine, or choline. In fact, such absolute barriers do not exist; rather, facilitated diffusion mechanisms operate which allow these compounds to enter the brain, and whose activities depend on plasma levels of their ligands.

C. The rate-limiting enzyme, within presynaptic nerve terminals, which initiates the conversion of the precursor to its neurotransmitter product must, similarly, be unsaturated with this substrate so that, when presented with more tryptophan, tyrosine, or choline, it can accelerate synthesis of the neurotransmitter. (Tryptophan hydroxylase and choline acetyltransferase [CAT] do indeed have very poor affinities for their substrates tryptophan and choline. As discussed below, tyrosine hydroxylase activity becomes tyrosine-limited when neurons containing the enzyme have been activated and the enzyme has been phosphorylated.)

D. The activity of this enzyme cannot be subject to local end-product inhibition, that is, the products of tryptophan's hydroxylation, 5-hydroxytryptophan and serotonin itself, may not appreciably suppress tryptophan hydroxylase activity, nor may acetylcholine levels within cholinergic nerve terminals affect CAT activity. Tyrosine hydroxylase activity probably is subject to some end-product inhibition when the enzyme protein is in its nonphosphorylated state; however, once the enzyme is phosphorylated, it apparently is freed from this constraint.

Available evidence suggests that only some of the neurotransmitters present in the human brain are likely to be subject to such precursor control—principally the monoamines mentioned above (serotonin; the catecholamines, dopamine, norepinephrine, and epinephrine; acetylcholine) and, possibly, histidine and glycine: Pharmacologic doses of the amino acid histidine do elevate histamine levels within nerve terminals (39), and the administration of threonine—a substrate for the enzyme that normally forms glycine from serine—can elevate glycine levels within spinal cord neurons (and may thus be useful for treating spasticity) (40).

One large family of neurotransmitters, the peptides, almost certainly is not subject to precursor control: Brain levels of these compounds have never been shown to change with variations in brain amino acid levels; moreover, there are sound theoretical reasons why it is unlikely that brain peptide synthesis would respond. The immediate precursor for a brain protein or peptide is not an amino acid, per se—as is the case for some of the monoamine neurotransmitters—but the amino acid molecule attached to its particular species of tRNA. In brain tissue, the tRNA-charging enzymes characterized to date have high affinities for their amino acid substrates (41), such that their ability to operate at full capacity, in vivo, is probably unaffected by amino acid levels (except, possibly, in pathologic states, like phenylketonuria, associated with major disruptions in brain amino acid patterns).

Little information is available concerning the possible precursor-control of the nonessential amino acids—like glutamate, aspartate, and gamma-aminobutyric acid (GABA)—which are probably the most abundant neurotransmitters in the brain, for the reason that it is very difficult to do experiments on these relationships. Even though glutamate and aspartate can be formed, at various organs in the body, via many different biochemical pathways, the precise pathways that synthesize these compounds within the terminals of neurons that use them as their neurotransmitters are not well established. In the case of GABA, although its precursor, glutamate, is well established, brain levels of that amino acid apparently cannot be raised experimentally without sorely disrupting normal brain functions: The macromolecule that transports acidic amino acids like glutamate and aspartate across the blood-brain barrier is unidirectional, and secretes these compounds by an active-transport mechanism from the brain into the blood (17). Hence, administration of even an enormous dose of monosodium glutamate will not affect brain glutamate levels unless it elevates plasma osmolarity to the point of disrupting the blood-brain barrier (42)—in which case experimenters find themselves with a different experiment from the one they had intended to perform.

If, indeed, the monoaminergic neurotransmitters plus glycine turn out to be the only ones subject to nutritional control, this will still provide the physician and the neuroscientist with a number of interesting mechanisms to explore and exploit: These same neurotransmitters are critically important in a large number of physiologic mechanisms and pathophysiologic states, and are thought to mediate the actions of many neuropharmacologic agents.

Effects of Methylation of L-dopa. Brain levels of

S-adenosylmethionine (SAM), the source of the methyl groups used by enzymes like catechol-O-methyltransferase (COMT) to O-methylate endogenous compounds like dopamine and norepinephrine, and drugs like L-dopa and alpha-methyldopa, are also affected by variations in plasma amino acid composition: Treatments that increase the plasma methionine ratio (the ratio of the plasma methionine concentration to the summed concentrations of the other LNAA) raise brain methionine levels, thereby increasing the substrate-saturation of the methionine-activating enzyme and the synthesis of SAM. This effect becomes potentially important to neurologists when trying to understand the consequences of prolonged treatment with large doses of L-dopa: The methylation of this drug can deplete the brain of SAM (43), thereby diminishing the brain's capacity to methylate a large number of endogenous substrates (ranging from the above neurotransmitters [44] to RNA and DNA). Administration of supplemental methionine protects against this depletion (45). The prolonged overuse of SAM to methylate exogenous L-dopa can also increase the brain's requirements for folic acid, a vitamin needed for the reconversion of homocysteine to methionine (46).

Receptor-Mediated Feedback and Neurotransmitter Release. In order for an increase in a neurotransmitter's synthesis, caused by administering a food or the transmitter's precursor, to affect its release, the neuron that releases it must continue to fire at its normal frequency. This may be kept from happening by receptor-mediated feedback processes which are activated soon after release of the transmitter has been increased: One such process involves presynaptic autoreceptors which are present on many monoaminergic terminals; some of the transmitter molecules within the synapse interact with the receptors, thereby reducing (by mechanisms not yet fully understood) the number of neurotransmitter molecules that are released by subsequent firings. The other process involves chains of neurons, including at least one that makes an inhibitory neurotransmitter: The precursor-dependent neurotransmitter now interacts with postsynaptic receptors, ultimately causing the neuron that releases it to receive fewer excitatory (or more inhibitory) impulses, and to fire less frequently. The fact that administration of tyrosine or choline to normal individuals produces few detectable changes in brain function can, as discussed below, be explained by the operations of these two feedback mechanisms. (Serotonin-releasing neurons apparently do not decrease their firing frequencies when brain tryptophan levels are increased, unless the increase transcends the normal range, which is quite broad. Hence, brain serotonin synthesis is always responsive to physiologic changes in brain tryptophan levels.)

Precursor Administration to Affect Neurotransmission. There probably are a number of situations in which receptor-mediated feedback mechanisms are not activated by increases in transmitter release, thus allowing precursor administration to affect neurotransmission. These might include:

A. Neurodegenerative disorders, which diminish the number of neurons (or presynaptic terminals) issuing from a precursor-dependent brain nucleus (for example, the substantia nigra in patients with Parkinson's disease.) The surviving neurons may exhibit increased firing rates (3, 26), which makes them more sensitive to the precursors, without affecting the precursor-responsiveness of other, intact, groups of neurons that happen to use the same transmitter.

B. Physiologic circumstances in which neurons undergo sustained increases in firing frequency (for example, sympatho-adrenal cells in hemorrhagic shock, which respond to supplemental tyrosine—by making and releasing more norepinephrine and epinephrine—as long as blood pressure remains low) (47).

C. Peripheral neurons which, unlike brain, lack multisynaptic feedback loops to be activated by increased local neurotransmitter levels. Thus, tyrosine administration enhances catecholamine synthesis in, and release from, peripheral sympathetic neurons (and chromaffin cells) in humans (48).

Choline administration (for 2–4 days) also persistently enhances acetylcholine release from splanchnic neurons (causing among other things, enzyme induction in the postsynaptic adrenomedullary chromaffin cells [49]).

D. Neurons which are components of positive multisynaptic feedback loops. In this circumstance, a precursor-induced increase in neurotransmitter release might be expected to cause further activation of the neuron that synthesized the transmitter, and, subsequently, an even greater ability to respond to supplemental precursor.

Tyrosine Effects on Dopamine and Norepinephrine Synthesis

Because tyrosine administration had not been shown to increase brain dopamine or norepinephrine levels in otherwise untreated animals, it was assumed until fairly recently that the catecholamine neurotransmitters were not under precursor control, in spite of the fact that plasma tyrosine levels do increase severalfold after protein intake or tyrosine administration (6, 50); that the LNAA transport system does ferry tyrosine, like tryptophan, across the blood-brain barrier (17); and that tyrosine hydroxylase, which catalyzes the rate-limiting step in catecholamine synthesis, is unsaturated in vivo (12). It seemed possible that a "pool" of neuronal dopamine or norepinephrine might exist whose synthesis was, indeed, responsive to tyrosine, but that this pool was too small, in relation to total catecholamine levels, to escape detection.

Hence, studies were performed to determine whether catecholamine synthesis or release, assessed independently of brain catecholamine levels, could be affected by changes in brain tyrosine concentrations. Catecholamine synthesis was estimated by following the rate at which dopa, the product of tyrosine's hydroxylation, accumulated in brains of rats treated acutely with a drug that blocks the next enzyme in catecholamine formation (aromatic l-amino acid decarboxylase); tyrosine administration increased dopa accumulation, while other LNAA decreased both it and brain tyrosine levels (12).

Catecholamine release was then estimated by measuring brain levels of metabolites of dopamine (homovanillic acid [HVA]; dihydroxyphenylacetic acid [DOPAC] or norepinephrine (methoxyhydroxyphenylglycol sulfate [MHPH-SO4]). Administration of even large doses of tyrosine had no consistent effect on these metabolites (51). However, if the experimental animals were also given an additional treatment designed to accelerate the firing of dopaminergic (52) or noradrenergic (53) tracts (dopamine receptor blockers; cold exposure; partial lesions of dopaminergic tracts; reserpine), the supplemental tyrosine now caused a marked augmentation of catecholamine release.

These initial observations formed the basis for the hypothesis that catecholaminergic neurons become tyrosine-sensitive when they are physiologically active, and lose this capacity when they are quiescent.

The biochemical mechanism that couples a neuron's firing frequency to its ability to respond to supplemental tyrosine involves phosphorylation of the tyrosine hydroxylase enzyme protein, a process that occurs when the neurons fire (54). This phosphorylation, which is short-lived, enhances the enzyme's affinity for its cofactor (tetrahydrobiopterin) and makes it insensitive to end-product inhibition (by norepinephrine and other catechols): these changes allow its net activity to depend on the extent to which it is saturated with tyrosine.

An additional mechanism underlying this coupling may be an actual depletion of tyrosine within nerve terminals, as a consequence of its accelerated conversion to catecholamines: If slices of rat caudate nucleus are superfused with a standard Krebs-Ringer's solution that lacks tyrosine or other amino acids, and are depolarized repeatedly, they are unable to sustain their release of dopamine; concurrently, their contents of tyrosine—but not of other LNAA—decline markedly. The addition of tyrosine to the superfusion solution enables the tissue to continue releasing dopamine at initial rates, and also protects it against depletion of its tyrosine (51).

The concentrations of tyrosine needed for these effects are proportional to the number of times the neurons are depolarized. (Of course, the intact brain is continuously perfused with tyrosine-containing blood, making it highly unlikely that tyrosine levels fall to a similar extent, even in continuously active brain neurons; however, they might decline somewhat, since tyrosine is poorly soluble in aqueous media, and diffuses relatively slowly.)

In recent studies, we have used the in vivo dialysis technique to assess effects of tyrosine on the release of dopamine from the rat's corpus striatum. When otherwise untreated animals receive the amino acid systematically, there is, after 20–40 minutes, a substantial increase in dopamine output, unaccompanied by detectable increases in levels of dopamine's metabolites DOPAC or HVA. But this effect is short-lived, dopamine release returning to basal levels after 20–30 minutes. This latter response probably reflects receptor-mediated decreases in the firing frequencies of the striatal neurons (to compensate for the increase in dopamine release that occurs per firing), or perhaps local presynaptic effects of the transiently-increased intrasynaptic dopamine levels. If animals are given haloperidol, a dopamine-receptor blocking agent, prior to or along with the tyrosine, the supplemental tyrosine continues to amplify dopamine output for prolonged periods.

The tight coupling of tyrosine responsiveness to neuronal firing frequency (and tyrosine hydroxylase phosphorylation) probably explains tyrosine's paradoxical effects on blood pressure:

The amino acid elevates blood pressure (and sympatho-adrenal catecholamine release) in hypotensive animals (47), but lowers blood pressure (without affecting sympatho-adrenal catecholamines) in hypertensive animals (55). (It fails to affect blood pressure at all in normotensive animals or humans [50]). Tyrosine's blood-pressure-lowering effect in hypertensive animals probably results from its conversion to norepinephrine in brain stem neurons, which, when active, suppress sympathetic outflow; these neurons presumably are activated in the varieties of hypertension in which tyrosine is effective, and may be participants in the brain's attempts to deal with the hypertension. As might be anticipated, tyrosine administration elevates brain levels of MHPG-SO_4 in these animals, but has little or no effect on brain MHPG-SO_4 in those with normal or low blood pressure.

Supplemental tyrosine may have useful effects in some patients with early Parkinson's disease (26) and in depression (given with or without 5-hydroxytryptophan or tryptophan [27]); its utility in treating hypertension or other cardiovascular diseases (such as cardiac arrhythmias) awaits evaluation. The amino acid may also have some value in the prophylaxis or treatment of stress responses: Rats subjected to a standard laboratory stress were found, immediately thereafter, to have depressed brain norepinephrine levels (particularly in the locus coeruleus and hypothalamus), probably reflecting the inability of norepinephrine's synthesis to keep up with its release; they also showed behavioral abnormalities and elevated plasma corticosterone levels. All of these changes, including the adrenocortical hypersecretion, were suppressed by supplemental oral tyrosine (56), but not if the tyrosine was coadministered with another LNAA (valine) that blocked its brain uptake.

Plasma tyrosine derives both from the tyrosine and the phenylalanine in dietary proteins, since the latter amino acid is hydroxylated to tyrosine in the liver. Phenylalanine itself can apparently serve as a substrate for tyrosine hydroxylase under special laboratory conditions, low concentrations partially sustaining dopamine release in the brain slice preparation discussed above when tyrosine is omitted from the medium. However, in higher concentrations (200 micromolar) and in the presence of normal tyrosine concentrations, phenylalanine inhibits tyrosine hydroxylase activity and suppresses dopamine release (51).

This inhibition might become clinically significant in people who consume very large quantities of the dipeptide sweetener aspartame. Unlike dietary proteins, aspartame lacks the other competing LNAA; hence, its consumption can cause major elevations in brain phenylalanine levels—especially if it is consumed along with foods that contain insulin-releasing carbohydrates (which, as discussed above, lower blood levels of the other LNAA) (57). Dietary proteins, unlike aspartame, fail to elevate and can actually lower brain phenylalanine levels, reflecting the fact that proteins contribute much more of the other LNAA than of the relatively scarce phenylalanine to the circulation. The clinical consequences of an aspartame-induced reduction in brain catecholamine synthesis might be anticipated from the known physiologic and behavioral roles of these neurotransmitters (e.g., maintaining the seizure threshold).

L-dopa, alpha-methyldopa, and 5-hydroxytryptophan are all LNAA, and like the naturally occurring LNAA in proteins, their brain levels depend not solely on their own plasma concentrations but also on their respective ratios to the other plasma LNAAs. If these drugs are taken with or soon after a high-protein meal, their uptake into the brain and their therapeutic efficacies will be diminished (1, 2, 58). This relationship may contribute to the "on-off" syndrome in parkinsonian patients receiving L-dopa.

Choline or Lecithin: Effects on Acetylcholine Synthesis

The amounts of acetylcholine released by physiologically active cholinergic neurons depend on the concentrations of choline available to them. In the absence of supplemental free choline, the neurons will continue to release fairly constant quantities of the transmitter (13); however, when choline is made available (in concentrations bracketing the physiologic range), a clear dose relationship is observed between its concentration and acetylcholine release (10, 13, 59). (The biochemical mechanism that couples a cholinergic neuron's firing frequency to its choline-responsiveness awaits discovery.) When no free choline is available, the source of the choline used for acetylcholine synthesis is the cells' own membranes (10, 13, 59). Membranes are very rich in endogenous PC, and this phospholipid serves as a "reservoir" of free choline (60), much as bone and albumin serve as reservoirs for calcium and essential amino acids.

It has been suggested that a prolonged imbalance between the amounts of free choline that are available to a cholinergic neuron and the amounts needed for acetylcholine synthesis might alter the composition of the neuron's membranes or its ability to make normal amounts of membranes to the point of interfering with normal neuronal functioning ("autocannibalism" [10, 61]). In that event, providing the brain with supplemental choline would serve two purposes: It would both enhance acetylcholine release from physiologically active neurons and replenish the choline-containing phospholipids in their membranes.

Neurons can draw on three sources of free choline for acetylcholine synthesis: that stored as PC in their own membranes; that formed intrasynaptically from the hydrolysis of acetylcholine (and taken back up into the presynaptic terminal by a high-affinity process estimated to be 30%–50% efficient in the brain); and that present in the blood stream (and taken into the brain by a specific blood-brain barrier transport system). PC in foods (liver; eggs) is rapidly hydrolyzed to free choline in the intestinal mucosa (or broken down more slowly, after passage into the lymphatic circulation). Consumption of adequate quantities of PC can lead to severalfold elevations in plasma choline levels, thereby increasing brain choline and the substrate saturation of CAT.

The phosphatidylcholine molecules consumed in the diet, as well as those formed endogenously in neuronal membranes, are heterogeneous with respect to their fatty-acid compositions. Some PCs (as in soy beans and nerve terminals) are relatively rich in polyunsaturated fatty acids; others (as in eggs) are highly saturated. PCs are also heterogeneous with reference to their mode of synthesis, brain neurons producing PC via three distinct biochemical pathways: the sequential methylation of phosphatidylethanolamine [PE]; the incorporation of preexisting free choline via the CDP-choline cycle; or the incorporation of free choline via the base-exchange pathway (in which a choline molecule substitutes for the ethanolamine in PE, or the serine in phosphatidylserine [PS]). Quite possibly, the different varieties of PC may subserve distinct functions; conceivably, one type of PC—distinguished by its fatty acid composition or its mode of synthesis—being preferentially utilized to provide a choline source for acetylcholine synthesis; or being formed preferentially during the processes of cell division or synaptic remodeling; or being involved in the pathogenesis of particular degenerative diseases afflicting cholinergic neurons (Alzheimer's disease) (61).

Supplemental choline or PC has been used with success in the treatment of tardive dyskinesia. A recent summary of related publications (62) concluded that choline and the cholinesterase inhibitor physostigmine were about equally efficacious, and that choline was less toxic. Most patients exhibited some improvement in the frequency of abnormal movements, but in only a few was there complete cessation of the movement (26).

Choline sources have also been tried in the treatment of Alzheimer's disease (cf ref. 63). Most well-controlled studies have treated subjects for relatively short intervals (6–8 weeks or less) and have focussed on younger subjects, with little or no success. A single double-blind study administered the PC for six months (64). Improvement was noted in about one-third of the subjects; the average age of the responders was 83, and that of nonresponders 73, a relationship thought to be compatible with evidence (65) that Alzheimer's disease may be more restricted to cholinergic neurons in subjects who become symptomatic at a later age. It seems important that additional long-term studies be done on the possible utility of PC in very old Alzheimer's patients.

Occasional reports have also described useful effects of choline or PC in treating mania, ataxia, and myasthenic syndromes (26). The general unavailability of purified PC for clinical testing clearly has, until recently, slowed evaluation of its utility.

Plasma choline levels are markedly elevated during the first postnatal week (66), probably reflecting immaturity of the hepatic choline oxidase enzymes; this provides rapidly growing cells with needed substrate for membrane PC formation. Choline levels were found to be reduced by almost half in athletes completing the Boston Marathon (67).

Conclusions

It appears well established that certain foods and pure nutrients can have important effects on nervous function, effectively modulating the neurotransmission mediated by serotonin, the catecholamines, and acetylcholine. Dietary amino acids or carbohydrates can also suppress or enhance the uptake of amino acid drugs (like L-dopa, L-5-HTP and alpha-methyldopa) into the brain.

Brain serotonin synthesis is directly controlled by the proportions of carbohydrate to protein in meals and snacks; these foods increase or decrease brain tryptophan levels, thereby changing the substrate saturation of tryptophan hydroxylase and the rate of serotonin synthesis. The release of the catecholamine neurotransmitters (dopamine, norepinephrine, and epinephrine), from physiologically active brain neurons and sympathoadrenal cells, is enhanced by tyrosine administration and diminished by the other LNAA, which compete with tyrosine for transport across the blood-brain barrier and neuronal membranes. Acetylcholine synthesis and release can likewise be amplified, in physiologically active neurons, by consumption of PC-rich foods.

The ability of serotoninergic neurons to have their output coupled to dietary macronutrients allows them to function as "sensors" of peripheral metabolism, and to subserve an important role in the control of appetite. However, it also makes the numerous other functions mediated by these neurons (sleepiness; mood) vulnerable to food intake, and may explain why some obese and/or depressed people overconsume dietary carbohydrates, perhaps using these foods as though they were antidepressant drugs (which also tend to increase intrasynaptic serotonin).

The robust and selective responses of catecholaminergic and cholinergic neurons to supplemental tyrosine and choline raise the possibility that these compounds (or tryptophan, for serotoninergic neurons) may become useful as a new type of drug—for treating diseases or conditions in which adequate quantities of the transmitter would otherwise be unavailable. If these nutrients turn out to have useful therapeutic properties, their utility will no doubt be enhanced by their familiarity to the body—which has no difficulty metabolizing large amounts of them overnight, without a trace; by the specificity that they derive by requiring the collaboration of individual neurons (which must both convert them to their neurotransmitter product and keep firing) to be effective; and by the ease with which their brain levels can be estimated from measurements of plasma composition. However, these advantages are counterbalanced by an obvious disadvantage in comparison with "real" drugs: They are much less potent (and, indeed, lack intrinsic potency at synapses).

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Mild Senile Dementia of the Alzheimer Type: Diagnostic Criteria and Natural History

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Abstract

The Memory and Aging Project of Washington University has established (1) the reliability and validity of clinical research diagnostic criteria for senile dementia of the Alzheimer type (SDAT), and (2) the reliability and utility of a staging instrument for the disorder, our Clinical Dementia Rating (CDR). A revision of the CDR is introduced. Problems and progress in quantifying the natural history of the disorder in a select sample are described. Issues are raised relevant to assessing the power of future intervention studies based on the natural history. A potentially useful approach is offered.

It is a pleasure to join with others in paying tribute to Professor Melvin D. Yahr in honor of his 70th birthday. His major academic interests have been the natural history of Parkinson's disease (PD) and how its manifestations are influenced by treatment. Diagnostic criteria for the disorder had been well established decades earlier, but Dr. Yahr and colleagues developed staging criteria (1) by which the natural history of the disease could be described and effects of treatment assessed. In many ways the investigations of senile dementia of the Alzheimer type (SDAT) by our research group have paralleled those earlier steps in PD.

The Memory and Aging Project of Washington University started as weekly meetings of the interdepartmental Dementia Study Group in 1972. In those early years the principal issue was the differentiation of normal pressure hydrocephalus from "degenerative" disease of the brain or "cerebral atrophy." A series of papers on related clinical and pathological topics resulted (2–10).

Following the pioneering work of Sir Martin Roth and colleagues in Newcastle (11) and of Drs. Robert Katzman and Robert Terry in New York (12), it became increasingly apparent in the mid-1970s that Alzheimer's disease (AD) was the principal cause of dementia not only in the presenile age group but also later in life. Both senile and presenile dementia are marked most often by the same lesions in the brain, neurofibrillary tangles and neuritic (senile) plaques. In the years since then, AD has been recognized as a major and increasing public health problem in the developed countries of the world (13).

We use the term SDAT or dementia of the Alzheimer type (DAT) to refer to the disorder when diagnosed by clinical and laboratory criteria without histological examination of the brain. The terms SDAT and DAT are analogous to "probable Alzheimer's disease" recommended by the NINCDS/ADRDA Work Group (14). AD refers to the disorder diagnosed on the basis of both clinical dementia and the characteristic histological features demonstrated by brain biopsy or postmortem examination.

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TABLE 1

Research Criteria for the Diagnosis of SDAT

I. Inclusion criteria (A through C must be present):
  A. Sustained deterioration of memory in an alert subject, plus impairment of cognitive ability in at least three of the following five categories:
    1. orientation
    2. judgment and problem solving
    3. function in community affairs
    4. function in home and hobbies
    5. function in personal care
  B. Gradual onset and progression
  C. Duration: 6 months or longer

II. Exclusion criteria (A through C must be absent):
  A. Other neurologic disorders, including parkinsonism, Huntington's disease, communicating hydrocephalus, progressive supranuclear palsy, infection, brain tumor, subdural hematoma, multiple sclerosis, stroke, multi-infarct dementia, seizure disorder, and brain trauma
  B. Psychiatric disorders, including primary affective disorder or major depression, schizophrenia, alcoholism or other substance abuse
  C. Other reversible dementias and other medical disorders that may reduce cognition, including overmedication, impaired function of lungs, heart, kidneys, or liver, anemia, hypothyroidism, vitamin B_{12} or folate deficiency, malignancy, and diabetes mellitus (if insulin-dependent or if more than mild in degree).

Until there is a validated biological marker for AD that does not require brain biopsy or autopsy, clinical investigations of SDAT require a valid, acceptable set of research diagnostic criteria and a system for staging the disorder as to severity. Recognizing the need for clinical investigations into the burgeoning public health problem of SDAT, we developed the necessary tools in 1977 while planning a longitudinal investigation of mild SDAT and its behavioral and biomedical correlates in comparison to those of healthy aging persons.

Research Diagnostic Criteria. Our plan was to enroll a group of elderly community-dwelling persons with mild SDAT who were free of other medical, neurological, and psychiatric disorders that might impair their cognitive function. We developed and published (15) the research diagnostic criteria given in Table 1. These criteria have been validated by finding the characteristic histologic features of AD in each of 25 SDAT research subjects who have come to postmortem examination (16).

These criteria are consistent with those for the diagnosis of "probable Alzheimer's disease" (14) and the DSM-III (17) diagnosis of primary degenerative dementia, Alzheimer type, but have the advantages of being linked to the staging instrument (see below) and being more specific because of more stringent exclusionary criteria. Greater specificity is important for many of the research issues to be addressed. The link to the staging instrument is helpful because it allows one to specify how much impairment must be present before a diagnosis of definite but mild SDAT is made, as opposed to even milder degrees of impairment, some of which might be considered part of the normal aging process.

Clinical Protocol. For both the research subject and an appropriate informant we developed a semistructured clinical interview which includes brief rating scales used previously by others. The Dementia Scale (DS) of Blessed et al (18) is a behavioral check list derived exclusively from questions asked of the informant and rates the patient on performance of everyday activities, changes in personal care, and changes in personality, interests, and drive. We also analyze data from that portion of the DS which assesses cognitive function in everyday activities and personal care, labelling that subscale as Dementia Scale/Cognitive (DSC). The Short Portable Mental Status Questionnaire (SPMSQ) of Pfeiffer (19) is a 10-item questionnaire posed to the subject. Language function is assessed by verbal tasks from the Boston Diagnostic Aphasia evaluation (20), grouped to form an Aphasia Battery (AB) useful for our purposes. We have also used the Face-Hand Test (FHT), administered and scored according to the method of Zarit et al (21).

Staging Instrument. The six cognitive abilities listed in Table 1 (memory plus the other five) represent the six categories of impaired cognitive function that form the basis of the staging instrument, the Washington University Clinical Dementia Rating (CDR), which provides a quantitative global assessment of dementia (22, 23). Even though each of the measures in the clinical interview leads to an individual score, none of these scores is used directly to calculate the CDR, which is instead derived by the clinical investigator using all information from both the structured and unstructured portions of the interview.

The clinician rates the subject on a 5-point scale of impairment (none = 0, questionable = 0.5, mild = 1, moderate = 2, and severe = 3) in each of the six cognitive categories. Only that impairment resulting from cognitive loss is scored, not that due to other factors, such as personality change or physical handicap. Allowance must be made by the clinician for those noncognitive factors before the CDR ratings are assigned.

TABLE 2
Clinical Dementia Rating (CDR)

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented in time, often to place	Oriented to person only
Judgment + problem solving	Solves everyday problems well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, differences	Moderate difficulty in handling problems, similarities, differences; social judgment usually maintained	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function at usual level in job, shopping, business and financial affairs, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home + hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly sustained	No significant function in home
Personal care	Fully capable of self care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

As discussed in our first paper on the CDR (22), we view it as a global assessment of the severity of dementia. For that reason it is effective in assessing the overall stage of a disorder such as SDAT. It does not rate other individual clinical phenomena of interest, such as apraxia, aphasia, depression, or personality change. Our position has been that scales incorporating data on those other aspects of behavior in dementia become so diverse that the scores derived can no longer be compared easily. For instance, a person who has only slight dementia but severe personality change or severe aphasia would attain the same score as one who has only moderate changes in all of those aspects of disordered function. Those other clinical elements not rated in the CDR are given separate ratings in segments of the interview protocol.

From the ratings in the six cognitive categories the global CDR is derived by published rules (22) and results in a rating of healthy (CDR 0), questionable (CDR 0.5), mild (CDR 1), moderate (CDR 2), or severe dementia (CDR 3). After a few years of additional experience with the CDR we recognized and eliminated minor ambiguities and published a revised CDR (23). Those changes did not influence our data materially; they made it easier to distinguish between CDR 2 and CDR 3.

In an early unpublished pilot study of 35 subjects with varying degrees of dementia, interrater reliability on the CDR was good, Pearson product moment $r = .89$. We have studied the reliability of the CDR among five clinical investigators recently (24) and again found it to be good (Kendall's tau B = .91; kappa = .74, weighted kappa = .87).

In order to increase the precison of description for the rating of questionable dementia (CDR 0.5) we are introducing another revision of the CDR (Table 2) which does not change materially the description of greater degrees of impairment.

Research Sample. After developing the research

TABLE 3

Characteristics of SDAT Sample (20 men, 23 women) and Control Subjects (28 men, 30 women)

	Mean	SD	Range
Age at entry, yrs			
SDAT	71.4	5.0	63.8–81.2
Control	71.7	4.9	64.3–82.5
Education, yrs			
SDAT	12.5	4.1	8–21
Control	12.8	3.5	7–20
Duration of SDAT at entry, yrs	3.5	1.7	0.9–9.0

diagnostic criteria, the staging instrument, the interview protocol, and plans for the longitudinal study, we enrolled 43 subjects with mild SDAT (CDR 1) and 58 healthy elderly control subjects (CDR 0). Using a videotape of the clinical interviews, a second experienced clinician agreed on the diagnosis of SDAT in each impaired subject and on the appropriateness of the designation of control subject. The problems inherent in recruiting subjects appropriate for research studies in this age group have been discussed (15, 25). A description of the sample was given in the first paper (15) of this series but is summarized in Table 3.

From our interdisciplinary studies a series of papers have resulted which characterized the mild SDAT subjects in comparison with their matched controls with regard to certain epidemiological data (26–28), language function (27, 29, 30), psychometric performance (31), affective symptoms (32), personality change (33, 34), apraxia (35), impaired activities of daily living (36), quantitative computed tomography (37), electroencephalography (38), and analysis of visual evoked potentials (39). Our investigators have also used this group of subjects to provide normative data for studies of cerebral blood flow and metabolism in aging by positron emission tomography and correction of those data for brain atrophy (40).

Natural History

Longitudinal studies of mild SDAT in comparison with healthy aging can be used to describe the natural history of both conditions. Our papers have described progression over time in psychometric measures (41, 42), overall CDR and clinical measures in the interview protocol (43), quantitative CT (44), measures of aphasia (30), and EEG (38), and the development of parkinsonism in our SDAT subjects after entry into the study (45).

Fiducial Point. What are appropriate methods of assessing the natural history of SDAT? One issue is the choice of the fiducial point (zero time point of reference). The time of onset of the disorder will remain uncertain because of the nature of the illness, even though many investigators record estimates of age at onset or duration of the disease. The time of diagnosis or first seeking medical advice is subject to many socioeconomic variables. One might use a defined point or narrow range on an assessment scale as a fiducial point, but that technique will be confounded by variability in the clinical presentation of mild SDAT and by measurement error. For fiducial point we chose entry into the study, because the SDAT sample was relatively homogeneous, in that they were selected by strict criteria, living in the community (not institutionalized), and restricted to the mild stage of the disease (CDR 1).

Changes over Time. The second issue has to do with methods of describing the course over time from the fiducial point. Milestones such as requiring full time supervision, placement in nursing home, or death have considerable face validity, but they depend on many variables (e.g., therapeutic, ethical, socioeconomic) that are both difficult to define and inconsistent across subjects and families. The choice of arbitrary points on assessment scales as milestones lacks face validity, because they are divorced from practical clinical value.

Methods of multivariate analysis and regression equations are yet to be explored, but the indices so derived may well be further removed from clinical relevance. Changes over time in an optimal group of predictor variables or in a group of scores on combined measures ("megascores") (46) remain for future consideration.

We have chosen tables of percentile scores and percentile plots similar to pediatric growth curves to describe group changes over time on relevant clinical measures (assessed at median times of 15, 34, 50, and 66 months after entry) as one quantitative technique (47) for approaching the natural history in SDAT (43).

Attrition of Subjects in Longitudinal Studies. The third issue is that longitudinal studies on impaired elderly subjects bear inherent problems (48). These include subject attrition (which may be selective), missing data, and heterogeneity. There are special problems in SDAT because of the severity of attrition due to death and other factors. Results are distorted because missing subjects include those who are more disabled and therefore unavailable for testing because of nursing home placement great distances away,

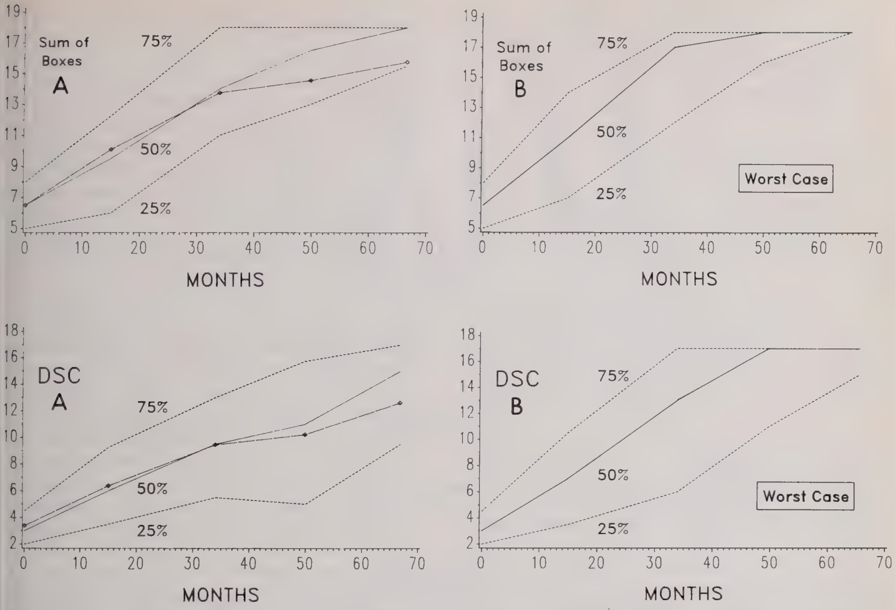

Fig. 1 and 2. Percentile plots over time in months after entry for scores (ordinate) on Sum of Boxes and DSC. (Rising lines = greater impairment; broken lines connecting diamonds = group mean scores.)

severe disability, or death. Data on the remaining subjects alone underestimate the progression of disability. We have approached that problem by providing data first on those who are tested and then by assigning a score of maximum impairment to those who are not tested.

As an example, Figure 1 illustrates SDAT group data on a useful clinical measure, the "Sum of Boxes," which is the sum of the ratings in each of the six cognitive domains ("Boxes") from which the CDR is derived (see Table 2). Maximum impairment on the Sum of Boxes is 6 × 3 = 18. Figure 2 provides group data similarly for the cognitive portion of the Dementia Scale (DSC). In each figure, data are presented in the left-hand panel ("A") on SDAT subjects available for rating and in the right-hand panel ("B") for the entire SDAT sample with untested subjects assigned maximum scores ("worst case"). That adjustment is justified because those untested had either died after advanced dementia or were severely impaired and under custodial care in locations too far away for us to reach them for testing (43).

"Spaghetti" plots describe the course of individual patients over time. Compare Figure 3 with Figure 1A, the percentile plot of the same data.

The malignancy of SDAT is emphasized by the rapidity with which these patients moved from the stage of mild dementia to moderate or severe dementia. Survivors were increasingly found to be severely demented (CDR 3), in that 67% of those surviving were severely demented at 50 mos after entry and 80% by 66 mos after entry (43). By five years after entry into the study, the cumulative rate of nursing home placement was 73% and that of death was 30%. The corresponding rates for 7 years after entry were 84% for nursing home placement and 44% for death, far greater than those for controls.

Only 4 of the 58 healthy control subjects deteriorated from CDR 0 to questionable dementia (CDR 0.5) during the 66-month period of the study (43). One of these died of an acute intercurrent illness shortly after the CDR 0.5 was recognized. The characteristic histologic signs of AD were evident at postmortem examination. With these exceptions, the control group maintained

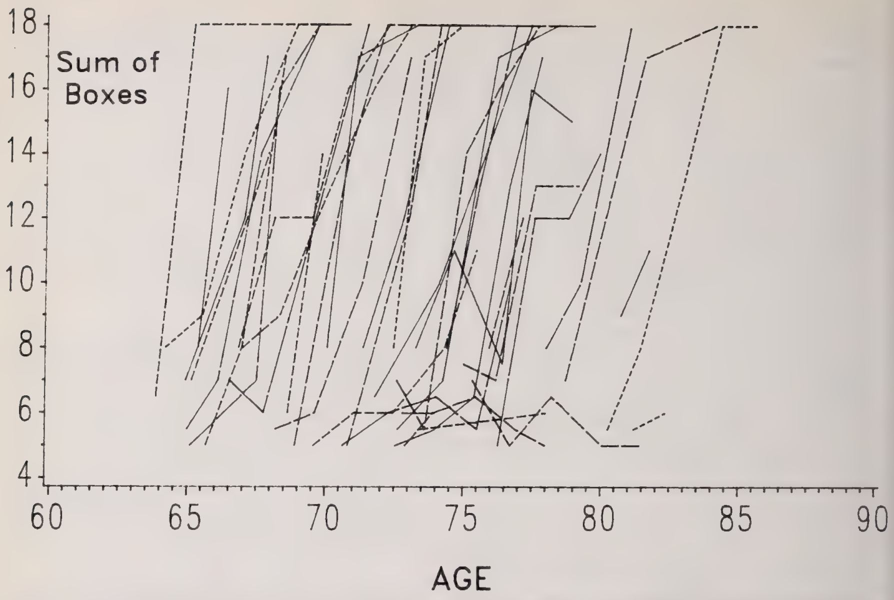

Fig. 3. Performance scores (ordinate) over time of individual SDAT subjects on Sum of Boxes. The lines of individuals are dispersed by being distributed according to their years of age (abscissa).

good performance on clinical and psychometric measures during the study.

Replication studies by our group are in progress.

Power of Intervention Studies

The quantitative study of the natural history of a disease offers the opportunity to examine the implications of proposed intervention strategies. The approach is similar to that used to advantage by the Clinical Investigation of Duchenne Dystrophy Group (49, 50). An important consideration in such planning is determining the power of the study (51), i.e., the probability that the study will declare the intervention strategies different one from another, or, expressed differently, the probability of detecting a true change in the natural history of the disease. Here the clinical investigator will require the talents of a biostatistician. Computations encompass the magnitude of the expected effect, the sample size, the significance level, and the power. For a particular study design (and associated statistical test) the investigator can specify any three of these parameters and solve for the fourth.

One of the most difficult steps is the selection of the magnitude of the expected effect. Several strategies can be proposed, but an attractive one for progressive diseases is a selection based on data about changes in a particular variable measured in a natural history study of patients similar to those who would be recruited into the proposed intervention study. From Table 4 we can see that the Sum of the Boxes had an average change of 3.62 units over the first 15 months following recruitment. This average change must be compared with the amount of variability in the change (which is related to the error term used in the statistical test). A simple difference score for Sum of Boxes (score at 15 months minus score at baseline) has a standard deviation of 3.70 (column 3 of Table 4). A standardized measure of the amount of change for a variable over a given period of time can be derived by dividing the average change by the standard deviation of that change (a measure of the heterogeneity of the changes across patients). The resulting measure, called "delta" (Δ), then can be used to compare the precision of different variables in tracking the progression of the disease. Table 4 shows the mean change, its standard deviation, and the associated delta for the clinical measures and four psychometric scales (31, 42). The clinical measures are described in the earlier section on Clinical Protocol. (Worsening performance is indicated by positive numbers for mean change with its delta for clinical measures and negative numbers for the corresponding values for psychometric measures.) Larger deltas add to the power of a study (see below). The WMS Logical Memory is included in Table 4 as an example of a measure with a small delta, resulting in this instance from the fact that many mild SDAT subjects had reached floor at the time of entry.

Statistical theory and experience indicate that the variability in the score values at the end of the period can be reduced by taking into account information in addition to the score on that variable at entry. To that end, one determines the root-mean-square error (RMSE), which is the square root of the variance of the observed values around their values as predicted by a multiple regression equation. Table 4 includes the RMSE for each variable at the end of the period when all of the variables shown in Table 4 at entry were used as predictors of the score at 15 months later. The associated deltas are also shown.

Note that the ranking of the variables (by size of their deltas) for following the progression of the disease does not necessarily correspond to the ranking of the same variables for differentiating mild SDAT from controls (31). Note also the RMSE is based on the entire ensemble of variables measured at entry; reducing the number of measures will generally increase the RMSE. Models that include only the given measure at baseline have RMSE values that lie between the standard deviation of the change score and the RMSE shown in Table 4.

Analysis of changes in group means over 15 months is justified because the changes in this progressive disease are substantially greater than the variability (interrater reliabilities, test-retest variability) in these measures. Because of attrition, data at times greater than 15 months after entry were less useful for describing the natural history via changes in clinical measures.

Consideration should also be given to whether the proposed intervention would affect all of the variables equally. For example, both the Aphasia Battery and the Boston Naming Test measure only a portion of the intellectual functioning of the patient and might be differentially affected as compared with the other variables.

Power will be dependent on multiple additional issues that influence the magnitude of the expected effect: Is there heterogeneity/subgrouping? Are there diagnostic errors? What is the interrater reliability? After one deals with these issues satisfactorily, calculation of the power then requires consideration of what the effect of the proposed intervention might be on each variable. It may be unreasonable to expect a treatment to reverse the progression of SDAT and lead to improvement in function. Arresting the progression of the disease would provide an expected difference between an untreated group and a treated group of the deltas shown in Table 4. Figure 4 illustrates the power (51) of such a trial for selected sample sizes using a delta of 1.0 (similar to that seen in Table 4 for Sum of Boxes, DSC, BNT) and a significance level of .05 by the one-tailed *t*-test.

TABLE 4

Indicators of Disease Progression for Each Measure from Entry to 15 Months Later

Measure	N*	Mean change	SD	Δ	RMSE	Δ
Sum of Boxes	39	3.62	3.70	0.98	3.02	1.20
DS	37	3.58	4.71	0.76	4.95	0.72
DSC	37	2.72	2.78	0.98	2.97	0.92
SPMSQ	34	1.53	2.02	0.76	1.40	1.09
AB	32	3.70	6.04	0.61	4.24	0.87
MC	29	−1.66	2.91	−0.57	2.52	−0.66
LM	29	−0.60	1.84	−0.33	1.53	−0.39
TM	24	−2.48	5.59	−0.44	5.84	−0.42
BNT	29	−6.03	5.79	−1.04	5.21	−1.16

MC and LM = Mental Control and Logical Memory subscales of the Wechsler Memory Scale; TM = Trailmaking A; BNT = Boston Naming Test.

* Number of subjects tested both at entry and 15 months later.

For the Sum of Boxes or another variable with a similar delta, one determines from Figure 4 that there is a 90% chance (power level 0.9) of detecting a 75% slowing in the rate of progression over 15 months if one has 33 comparable patients each in the treatment and placebo group. Only 19 patients in each group would be required to detect a complete arrest of the disease (100% slowing) in 15 months with the same level of power. However, it would require 72 patients in each group to offer a 90% chance (same power) of detecting a 50% slowing in the rate of progression.

One of the additonal uses of a database for describing the natural history of the disorder will be the development of clinical prediction rules (52), another means by which therapies may be chosen and evaluated. This procedure will follow the steps that we have discussed to this point.

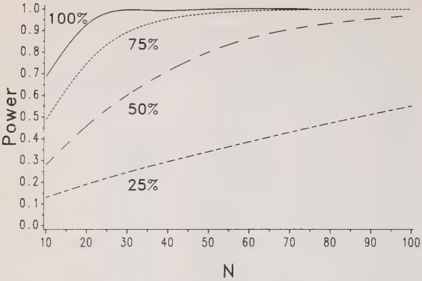

Fig. 4. Graph relating power of study (ordinate) and sample size (abscissa) of each group (treatment and placebo) to degree of reduction in rate of progression of disease, ranging from complete arrest (100% reduction) through lesser degrees of slowing.

Present Status

Those of us studying AD and SDAT have a long way to go before we have reached the stage of understanding of these disorders comparable to that which exists already in our understanding of Parkinson's disease. We have come to general agreement on diagnostic criteria, some useful for research purposes and others useful for general clinical application. There is no consensus on how to stage DAT or SDAT. Our instrument, the CDR, has proved useful and reliable for us. It has been put to use by several other groups (53–56) and has been recommended by others (57–59) who have reviewed the subject. Other staging instruments are being used by others (60–65).

Multiple groups of investigators have approached the documentation of the natural history of DAT/SDAT using a variety of methods. Studies based on autopsy-confirmed samples (66-68) provided little longitudinal clinical information. The clinical longitudinal papers (55, 69–77) lack sufficient data on histological confirmation.

Note that similar investigations of Parkinson's disease by multiple groups of investigators still use a variety of staging instruments and scales for quantification of the disabilities in that order. Unanimity has not been reached in the two decades since Dr. Yahr published his scale for assessing disability in Parkinson's disease (1).

The many investigators studying AD/SDAT have yet to agree on the clinical measures useful for long-term assessment. To be sure, there is strength in having multiple measures used by different investigators. When the same substantive pattern of longitudinal results is observed across various measures used by different investigators, one can have greater faith in the validity of the pattern.

Rates of change on clinically relevant assessment scales are meaningful (47), provided the steps of the scale are relatively uniform (interval scale) or that patients enter the study at the same point on the scale. Change scores in the measures used here over the 15 months after entry provided useful information regarding clinical progression in a carefully selected sample of subjects with mild SDAT. As compared with the other clinical measures (Table 4), global cognitive measures of impairment (Sum of Boxes and the Dementia Scale/Cognitive) showed greater consistency in those change scores.

With these observations and those of others, we are witnessing the infancy of the quantitative study of the natural history of SDAT. Preparations are just being started to lay the groundwork for proper assessment of future interventions to slow or halt the progression of the disorder.

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Iron in the Brain: Implications for Parkinson's and Alzheimer's Diseases

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Metals have always been implicated in the pathogenesis of neurologic and psychiatric disorders (1). Parkinson's disease and Alzheimer's disease have not escaped such scrutiny because metals promote the formation of excess and highly reactive free radicals, which in turn can induce membrane fluidity and degeneration by the process of lipid peroxidation (2a, 2b, 3). Such a phenomenon has on several occasions been implicated as intimately involved in these two neurodegenerative disorders (4, 5).

Here I explore, with good reason, the role of iron in brain biochemistry and function. Why particularly iron? It is one of the few metal ions whose role in the central nervous system has received little attention, even though it is important in many enzymatic metabolic and structural processes (6). Thus, an abnormality in iron availability, either excess or deficiency, would be expected to have profound effects on this organ. Iron deficiency and iron overload are among the most prevalent nutrient disorders known to involve a metal. The vast literature dealing with their consequences on systemic organs has not included much attention to such effects on the brain until recently (7, 8).

Iron in the Brain

Iron is the most abundant metal in earth crust and in the body. As much as 40 mg/kg body weight of this metal is present in humans and animals for utilisation in metabolic processes. In the brain, iron content is low at birth but increases with age during the first decade of human life and the first four weeks in rats. Thereafter it remains constant, although in human striatum it is thought to increase up to the age of 30. The brain has roughly one quarter of the iron found in the liver. However, this is not a true reflection of the status of brain iron, since there are large differences between the various regions (see later discussion). The turnover of iron in the brain is significantly slower than in the liver (9, 10). Thus, in nutritionally iron-deficient (ID) rats, it is the liver stores that are almost totally depleted, with a moderate (40%) reduction in the brain. In the same vein, iron supplementation of ID animals results in restoration of liver iron within seven days; by contrast, that in the brain takes two to three weeks. While liver iron stores can fluctuate as much as twentyfold without any physiologic side effects, the brain iron cannot be increased beyond what is normally found. This would indicate a regulatory system for the transport of iron into the brain, at present poorly understood.

The most notable aspect of iron in the brain is its uneven distribution, unlike any other metal (zinc, copper, manganese, magnesium). The earlier studies of Spatz (11), confirmed subsequently by others and us (7, 12), show that in the human brain, iron concentration varies in four structural groups. The highest concentrations are found in globus pallidus and substantia nigra, which may contain as much as 200 μg/g tissue. The second highest concentrations are in the red nucleus, caudate nucleus, putamen thalamus and subthalamus, and dentate nucleus and dentate gyrus. The third group includes the cerebral cortex, cerebellum, anterior thalamus, mamillary body,

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central gray. The lowest iron content is found in medulla oblongata, gray matter, spinal cord, and spinal and sympthatic ganglia. The iron content of globus pallidus, substantia nigra, putamen, and red nucleus is as high as or higher than that in the liver, the organ responsible for disposition of the metal.

There have been few studies on iron distribution in animal brains. However, recently Hill and Switzer (13), using an adapted histochemical technique for detection of iron, have elegantly demonstrated that what is true for iron distribution in human brain is also valid in rat brain. The highest iron concentrations were detected in globus pallidus, substantia nigra, interpeduncular nuclei, and dentate gyrus. We have substantiated these data in monkey brain using biochemical method for 6-iron detection (14).

The most obvious question to be asked is, what is the purpose of such large iron content in the globus pallidus, substantia nigra, and dentate gyrus? Insight is not easily forthcoming. However, while seeking an answer, one cannot fail to note the coincidence of the areas primarily affected in Parkinson's disease, Huntingdon's chorea, Alzheimer's disease, and Hallervorden-Spatz disease with areas rich in iron and dense neurotransmitter innervation, (GABA) dopamine, serotonin, and acetylcholine.

Brain Iron and Dopaminergic Sensitivity

The high concentration of iron in some brain regions is quite puzzling. At best the enzymes, oxidative processes, and proteins would require roughly about 5%–10% of the total iron present. Whether the rest acts as a storage reserve or has structural or other functional purposes is hard to say. What is clear from our recent studies is that the normal amount of iron in the brain may be crucial for maintaining the function of dopaminergic and GABAergic neurotransmission (8, 15–17). The globus pallidus not only receives a dense GABA input from striatum but contains the highest concentration of GABA. Substantia nigra, par reticulata receives GABA input from both pallidum and striatum. And, of course, dopamine cell bodies give rise to the dopamine neurons of striatum.

In the past ten years we have examined the effect of alteration in brain iron content on the latter two neuronal systems. These studies arose from reports that iron-deficient subjects (adults and children) and animals are hypokinetic and show abnormal behaviours (18). Although we appreciated that the hypokinesia may stem from a reduction in oxygen-carrying capacity in muscle resulting from anemia (18), there was reason to believe that brain function may be affected at the level of dopamine neurotransmission. At best it was thought there would be a reduction in the activity of iron-oxygen dependent tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis (19). Although iron-deficient rats were shown to have lower brain iron and diminished behavioral responses to monoamine oxidase inhibitor plus L-dopa or apomorphine, their tyrosine hydroxylase activity and turnover of dopamine were unaltered (20). The subsensitivity of apomorphine-induced behavioral response is now recognized to be associated with the reduction of dopamine D_2 receptor Bmax (dopamine receptor subsensitivity) as identified with ^{3}H-spiperone binding in membranes prepared from caudate nucleus of iron-deficient rats (21). The reduction of dopamine D_2 receptor number in iron-deficient rats can be reversed by iron supplementation when brain iron content is restored to normal.

However, neither dopamine D_2 receptor number nor brain iron content can be increased beyond their original values (10). This phenomenon is thought to be related to the breakdown of blood-brain barrier (BBB) during iron deficiency, allowing the uptake of iron to take place (22). Once BBB is formed as a result of the correction of iron deficiency, no further increase in brain iron or dopamine D_2 receptor can occur. By contrast, intraamygdalae (23) or intraventricular injection (16, 17) of $FeCl_3$ induces a time-dependent (1–3 weeks) dopamine D_2 receptor supersensitivity, as indicated by the increase of ^{3}H-spiperone binding in caudate nucleus and behavioral responses to apomorphine. Iron is now thought to play a major role in the synthesis of dopamine D_2 receptor (7). Electrofocusing and two-dimensional SDS-gel electrophoresis of proteins from iron-deficient caudate nucleus and nucleus accumbens have shown the reduction of a 94K dalton molecular weight protein subunit (24, 25), which is identical to the subunit of purified receptor (26).

The other consequences of intracerebral injection of iron are well-known: degeneration of GABAergic neurons and extensive membrane lipid peroxidation (27). It is the latter aspect that has aroused much interest, because it involves the generation of "oxygen radicals" as mediators of the action of certain neurotoxins. The use of antioxidants as a treatment of degenerative disease of the nervous system is now considered a real possiblility (2a, 2b; see article by Kopin).

Oxygen Radicals and the Nervous System

Parkinson's Disease. In this short and noncomprehensive review, I confine my remarks to the role of iron. Metals, especially Fe^{++}, have always been suspected of playing a role in cytotoxicity and cell degeneration (2a, 2b). The basal ganglia, by virtue of its high lipid, oxygen consumption, elevated metals (e.g. iron) and enzyme metabolic activities, is ideal for degeneration as a result of the action of free radicals (3, 7, 28). This would make it highly susceptible to the cellular degenerative action of lipid peroxidation (2b). For this reason, the essential role of metals in promoting free-radical formation from hydrogen peroxide suggests that a study of their metabolism in Parkinson's disease and Alzheimer's disease is important to the understanding of the underlying cause of these degenerative processes. It is the excessive hydrogen peroxide, known to be formed in the brain (especially in basal ganglia) when in contact with reduced transitional metals (Fe^{++} and Cu^{+}) that liberates free radicals, such as the highly reactive cytotoxic hydroxyl radicals ($\cdot OH$). The latter in turn induces the lipid peroxidation, increased cell membrane fluidity, and finally the cell degeneration processes (2b). This phenomenon is now considered to be the basis of neurogenerative action of certain neurotoxins.

Cotzias (29) attempted to develop an animal model of Parkinson's disease using excessive manganese in rodents, with little success. Although the biochemical data generated pointed to some form of abnormality from neurotoxicity studies with manganese in rats and human subjects, a definite role for it in the pathophysiology of Parkinson's disease has yet to be revealed (3). This does not necessarily exclude the role of one or a combination of other metals either directly or indirectly. Earlier studies had indicated that iron was consistently increased by a factor of two or more above control values in caudate nucleus and globus pallidus of parkinsonian brains (30). Our own analysis of brain iron, copper, zinc, magnesium, and calcium clearly showed no profound differences between the concentrations of these elements in control and parkinsonian brains (12). However, a significant increase of ferritin was observed in the substantia nigra and globus pallidus. More recently, Dexter et al. (31) have reported an increase of iron as well as copper in parkinsonian brain. The reason for the discrepancy in our studies and those of others is not known, but may be related to the procedures used for metal analysis. These included histochemical, biochemical, and atomic absorption methods of iron analysis. Even if future studies do establish that there are no fundamental alterations of metal (iron) content in parkinsonian brain, studies of the role of iron in brain biochemistry need not be neglected. It is not necessarily the change in the concentration of iron which could be important, but rather the availability of free iron.

The implications for the discovery of MPTP (N-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine), is that Parkinson's disease may be related to a neurotoxic event involving a cytotoxic compound similar to MPTP (32; see article by Kopin). Paraquat, diquat, and MPTP are pyridine-derived cytotoxic substances having similar structures and respectively causing lung toxicity, lesion of lens, and parkinsonism in humans and animals. The prevailing evidence to date is that paraquat and diquat mediate their cytotoxic activity via lipid peroxidation with the specific involvement of iron (33). It has recently been demonstrated that iron greatly potentiates the toxicity of paraquat in mice, and that iron-chelator desferrioxamines prevent this effect (34). The paraquat radical and the cation free radicals of the closely related chemicals diquat and benzyl viologen mediate a rapid and complete release of iron from ferritin, without altering ferritin structure. These studies have indicated that release of free iron from ferritin (the iron storage protein) contributes significantly to free-radical-mediated toxicities (33). The structural similarities of MPTP and its MAO-B promoted metabolite, MPP^{+}, to the above compounds led Barbeau et al. (28) and Youdim (35) to examine their dopaminergic neurotoxicity in vitro and in vivo in relation to iron. The results indicated that transitional metals, namely iron, were important in the neurotoxic action of MPTP, because iron chelation agents prevented its toxicity and the depletion of dopamine. Iron potentiated the autooxidation of dopamine and oxidation of MPTP, thus contributing to further potentiation of dopamine autooxidation (28). In this instance MPTP might derive the iron redox equilibrium in order to release Fe^{+++} from ferritin and produce oxygen radicals ($O\text{-}_2$) similar to the reaction of paraquat. The situation may be further complicated by the formation of cytotoxic hydroxyl radicals ($\cdot OH$) from the interaction of freely available reduced iron with the H_2O_2 (Fenton reaction) formed from the oxidation of MPTP by MAO-B in the striatum. The metabolically active basal ganglia produces a significant amount of H_2O_2 from the reaction of monoamine oxidase (28). H_2O_2 itself has the ability of reversibly inducing MAO-B activity in human and rat brain (36). This situation may arise where positive feedback stimulation of MAO-B may lead to a further formation of H_2O_2 and excessive amounts of free hydroxyl radical (·OH).

Factors other than those discussed that may also contribute to degenerative processes in Parkinson's disease are overproduction or decreased breakdown of H_2O_2 and decreased availability of antioxidants for rapid removal of oxygen radicals ($O\text{-}_2$ and ·OH). The most effective enzyme responsible for the decomposition of hydrogen peroxide and prevention of cellular damage is catalase. This enzyme is absent from the brain (37). However, glutathione peroxidase, which also decomposes H_2O_2, is present, but its activity is highly dependent on the availability of reduced glutathione (38). Therefore, it may be expected that where excessive amounts of H_2O_2 are available the basal ganglia would be rendered susceptible to damage from free radicals, formed as a result of iron-H_2O_2 interaction (Fenton reaction).

Ascorbic acid, the most powerful physiologic antioxidant, present in high concentration in the basal ganglia, is considered to have dual effect in vivo. It can not only promote radical reactions, but can also interact quickly and effectively with $O\text{-}_2$ and ·OH radicals, rendering them inert. Hence, at low concentrations it acts as a prooxidant and at high concentrations as an antioxidant (2). Significant decreases of glutathione and ascorbic acid have been observed in globus pallidus, substantia nigra, and putamen in parkinsonian brains (12), confirming earlier reports (39, 40). This led Perry et al. (40) to suggest that Parkinson's disease may be a disorder associated with glutathione deficiency of substantia nigra. MPTP, the dopaminergic Parkinson-inducing neurotoxin, causes depletion of glutathione in the substantia nigra, which is prevented by pretreatment with the antioxidant ascorbic acid (41). The morphologic and biochemical changes induced by MPTP and buthionine sulfoxine, an intracellular inhibitor of glutathione, are remarkably similar (42).

The implications of these studies for future approaches in retarding or even preventing the progressive neurodegenerative aspects of Parkinson's disease are clear. The clinical use of antioxidants, even iron-chelating agents which would cross the blood-brain barrier, and/or monoamine oxidase (MAO) B inhibitors such as 1-deprenyl or AGN 1135) having the ability to selectively inhibit MAO-B in the basal ganglia in vivo and preventing the formation of H_2O_2, can now be considered a rational approach. In one retrospective study, long-term 1-deprenyl treatment has been shown to increase the survival rate of parkinsonian patients (43, 44). The latter results need clear assessment.

Alzheimer's Disease and Brain Iron. Considerable attention has been paid to aluminum as a possible causal factor in senile dementia, since a significant elevation of this metal has been reported in such brains (45). The role of aluminum in this disease is still unclear, even though the metal has been localized in neurofibrillary tangles containing neurons (45–47). No other element was noted to accumulate in the tangle-bearing neurons to the degree seen with aluminum. Even so, iron has been found to be increased within or near neuritic plagues (48, 49). This finding could be of paramount importance because both human and rat dentate gyrus (Amos Horne) have extensively high concentrations of iron (7, 13). Iron has the ability to promote membrane lipid peroxidation but aluminum does not (50). Halliwell and Gutteridge (50) have recently demonstrated that in vitro aluminum has extensive synergistic action (1500%) on the lipid peroxidation induced by iron. The mechanism of this synergism is not known but may be related to the formation of free radicals. Whether such a phenomenon can occur in vivo as a result of a neurotoxic event is a subject for future studies. Further studies on the state of both iron and aluminum in the Alzheimer brain are necessary. Normally iron in tissues is stored in inactive forms as ferritin. It is the availability of free iron which is thought to bring about the cytotoxic reactions.

Conclusion. Clearly, iron may have a special function in the brain. It remains to be seen how the metal is transported into the brain and selectively deposited in neurotransmitter-rich regions. Whether iron therapy would be of significant value, at least in Parkinson's disease, as Birkmayer and Birkmayer (51) have suggested, needs clarification, because iron does not pass the blood-brain barrier. Its beneficial effect, if any, cannot be attributed to a central action, because animal studies have clearly shown modulation of dopaminergic neurotransmission by this metal to be a long-term process (8).

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Neuropeptides in Alzheimer's and in Parkinson's Disease

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Alzheimer's disease (AD) and Parkinson's disease (PD) encephalopathies with high prevalence (AD = 3–10/1000, PD = 1/1000 in the general population) present some clinical similarities.

In AD a slight striatal hypertonic syndrome is usually observed in advanced cases (1–3). In PD, dementia occurs in 30% of cases (4, 5).

Neurotransmitter alterations also present some similarities between these two diseases. Dopamine (DA) of the nigrostriatal system decreases very significantly in PD and slightly in AD (6, 7). Acetylcholine (ACh) of the basocortical system decreases very significantly in AD and less in PD with dementia even without senile plaques (PS) and neurofibrillary tangles (NFT) (8–10).

In this paper we relate recent data in the literature on neuropeptides in AD and in PD and our own morphologic observations on substance P (SP), somatostatin (SOM), and neuropeptide Y (NPY) in these diseases. We try also to discuss hypothetical relationships between some neuropeptidic changes (SOM,SP) and the alterations of other neurotransmitters [ACh, glutamate (Glu), GABA, DA, glycine (Gly)].

Neuropeptides: Recent Data

Substance P (SP). The morphological mapping in the whole human brain of SP axons and terminals using standardized immunohistological methods (11, 12) was first realized by our group in Geneva (13) and completed by the same group by mapping of SP-cell bodies (14, 15).

We observed the presence of SP in the following areas: (a) somatosensory systems of spinal cord and brain stem (nociceptivity); (b) hippocampus and neocortex:intrinsic SP-cell bodies and terminals (memory? other cortical functions); (c) caudate nucleus and putamen: SP-perikarya from which SP axons reach the globus pallidus, where peridendritic synaptic SP terminals form "Pipe-shaped" structures, and in the substantia nigra, where terminal SP axonal varicosities establish synaptic connections with large DA-melanin-cell bodies and small Gly-cell bodies (extrapyramidal functions); (d) medial habenular nucleus: SP cell bodies from which SP axons reach the interpeduncular nucleus (limbic regulations); (e) SP-cell bodies and terminals in the amygdala, superior colliculus, mesencephalon, and raphe nuclei.

Alzheimer's Disease. Our morphological observations (16–18) are the following: (a) decrease of the immunological staining of SP in the hippocampus (Fig. 1b); (b) SP-positive amorphous material inside the senile plaques (PS) or in their corona (in about 5% of PS); (c) increase of the SP-immunological staining in the globus pallidus (Fig. 1d) and in the substantia nigra (Fig. 2b).

Our morphologic observations are in agreement with those of Grafe et al. (19). Other studies have shown by RIA that SP is decreased in the hippocampus and neocortex from 32% to 57% (20) or from 30% to 40% (21); increased (+88%) in the putamen, decreased (−25%) in the septal nuclei (22), decreased in the CSF (23).

The cortical decrease of SP is more important in the presenile than in the senile form of AD (21).

Parkinson's Disease. The amount of SP is significantly decreased in the substantia nigra (−30%) and the globus pallidus (24–27). It seems, however, important to distinguish, con-

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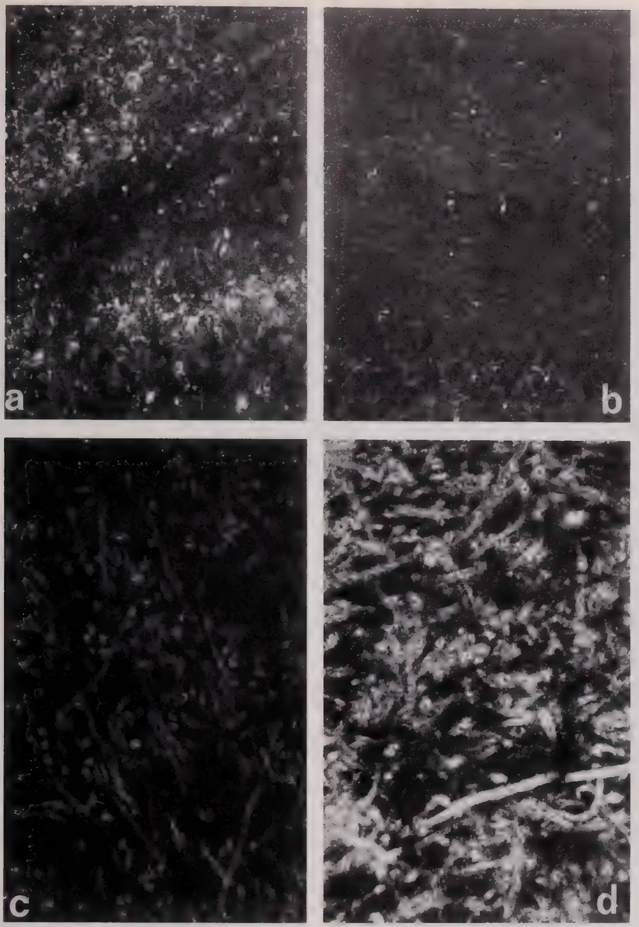

Fig. 1. Substance P of hippocampus and globus pallidus in Alzheimer's disease. **Left (a, c)**: control; right **(b, d)**: AD. **Top (a, b)**: hippocampus, **below (c, d)**: globus pallidus. Hippocampus: decrease of density of axonal SP varicosities and of intensity of their SP immunologic reaction. Globus pallidus: increase of SP immunologic reaction in peridendritic axons (pipe-shaped structures). (Coon's method, fluorescence microscopy; hippocampus ×220, globus pallidus ×540.)

cerning nigric SP (a) PD cases demented and nondemented because nigric SP increases in Alzheimer dementia, and (b) PD cases treated and nontreated, because L-dopa might interest with peptidergic transmission and modulate the level of presynaptic peptidergic content (25). These remarks may explain the spread of results concerning nigric SP in PD: unaltered SP distribution (19, 28), slight increase in PD with dementia (29, 30) or important decrease in PD without dementia (Fig. 2c). In other areas (cerebral cortex, hippocampus, hypothalamus, amygdala, caudate, putamen, and nucleus accumbens) there is no change in SP distribution (21, 26, 27).

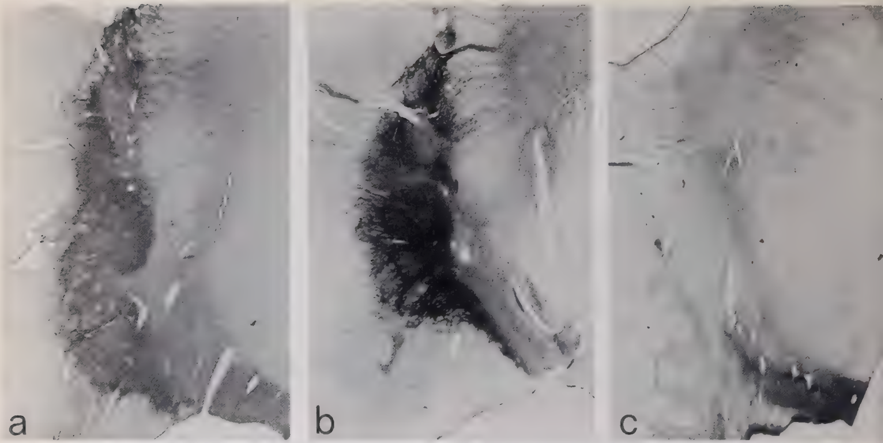

Fig. 2. Substance P of substantia nigra in Alzheimer's disease (AD) and Parkinson's disease (PD). **a**, control; **b**, AD; **c**, PD. SP immunologic reaction increases in AD and decreases in PD. (Peroxydase-antiperoxydase method ×8,9.)

Somatostatin (SOM). We have studied morphologically the distribution of SOM in the human brain and realized its mapping (14, 31, 32). SOM-cell bodies, and SOM varicosities in axons and terminals are observed in the following regions: archeopaleo- and neocortex; subcortical white matter (frontal, parietal, and temporal); accumbens and caudate nuclei, putamen, hypothalamus, reticular nuclei of the thalamus and of the brain stem, amygdala, substantia innominata, and basal nucleus of Meynert (BNM).

SOM inhibits the release of growth hormone (GH), exerts an inhibitory action on some central neurons (33), and an excitatory action on the hippocampus (34). SOM is excitatory on the cholinergic neurons of the substantia innominata in the BNM: the intraventricular administration of SOM stimulates cholinergic neurons of the BNM and enhances the release of ACh from cortical cholinergic terminals (35).

Alzheimer's Disease. Our morphological observations (16, 17, 36–38) are the following: (a) hippocampus: decrease of the number of SOM cells, axonal and terminal SOM varicosities and of their SOM immunologic reaction (Fig. 3b); (b) neocortex; decrease of the number of SOM-cell bodies from which some are shrunken; decrease of the density of axonal and terminal SOM varicosities in all the cortical layers, especially in the superficial layers and decrease of their immunological reaction; (c) decrease of the number of SOM neurons in the subcortical white matter, at the frontal, parietal, and temporal areas.

The extent of these changes is parallel to the severity of the cortical degeneration (PS and NFT density); (d) SOM amorphous material inside or around the PS (in about 20%) (Fig. 5a) (e) NFT in some SOM-cell bodies; (f) amygdaloid nuclear complex: slight decrease of the density of SOM axons and terminals; (g) septal nuclei: reduction of SOM neurons and axons; (h) mammillary bodies: slight decrease of SOM axons; (i) caudate nucleus, putamen, and thalamus: no changes; (j) substantia innominata and BNM: increase of the density of the axonal and terminal SOM-varicosities and increase of their SOM-immunological reaction (Fig. 3d).

These morphologic observations corroborate results obtained by RIA:

(a) cortex: decrease of SOM from 47 to 68% (22, 39–47). The decrease of cortical SOM is more pronounced in the presenile form of AD (48), and is accompanied by a correlative decrease of the number of SOM cortical receptors, probably due to a transneuronal degeneration (49).

(b) subcortical nuclei: decrease (−56%) in septal nuclei; light but nonsignificant decrease in amygdaloid nuclei; no change in caudate nucleus, putamen, and thalamus; important increase (+108%) in the substantia innominata and in the BNM (22).

(c) CSF: decrease of SOM (50–54) SOM in CSF

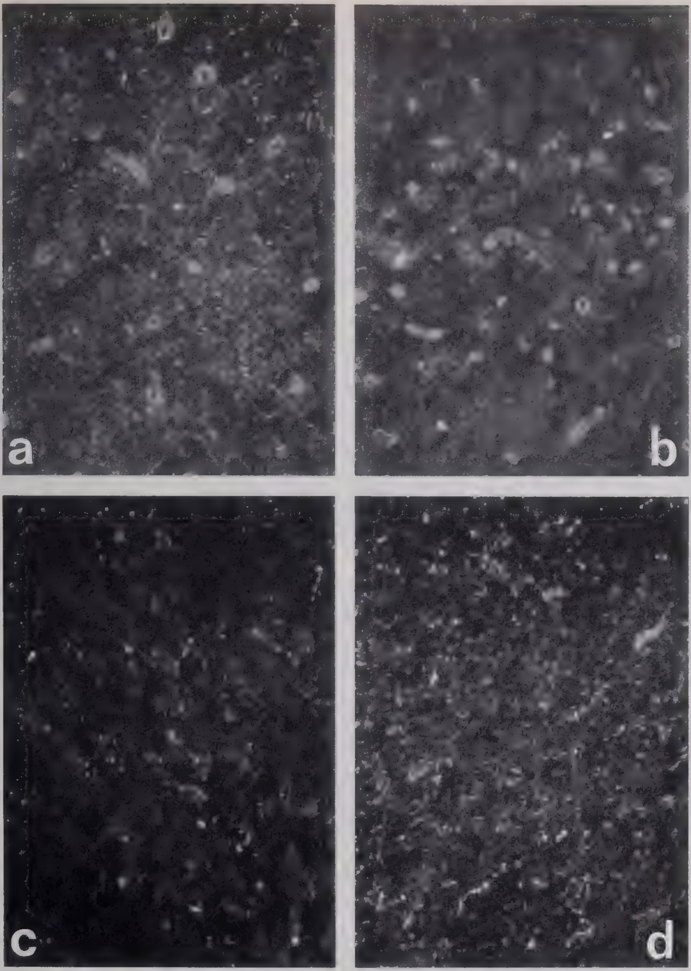

Fig. 3. Somatostatin of the hippocampus and basal nucleus of Meynert (BNM) in Alzheimer's disease (AD) **Left (a, c)**: control; **right (b, d)**: AD. **Top (a, b)**: hippocampus; **below (c, d)**: BNM. Density of axonal SOM varicosities (granules) and intensity of their SOM immunological reaction decrease in hippocampus (**b**) and increase in BNM (**d**). (Do not take into account nonspecific fluorescence of capillaries and of other nonaxonal structures). (Coon's method, fluorescence microscopy; hippocampus ×570, BNM ×540.)

seems to be due to a dispersed release, essentially cortical (55). The decrease of SOM in CSF means that the reduction of the cortical SOM is not due to an excess of release (SOM hyperactivity), but is related to the degeneration of SOM fibers and neurons (SOM hypoactivity).

Parkinson's Disease. A decrease (30%–50%) of SOM is found in hippocampus and neocortex (5, 25, 27). Like the ACh cortical deficiency, SOM cortical reduction in PD is linked to the dementia process. In PD without dementia SOM levels are normal and reduced in PD with dementia (56).

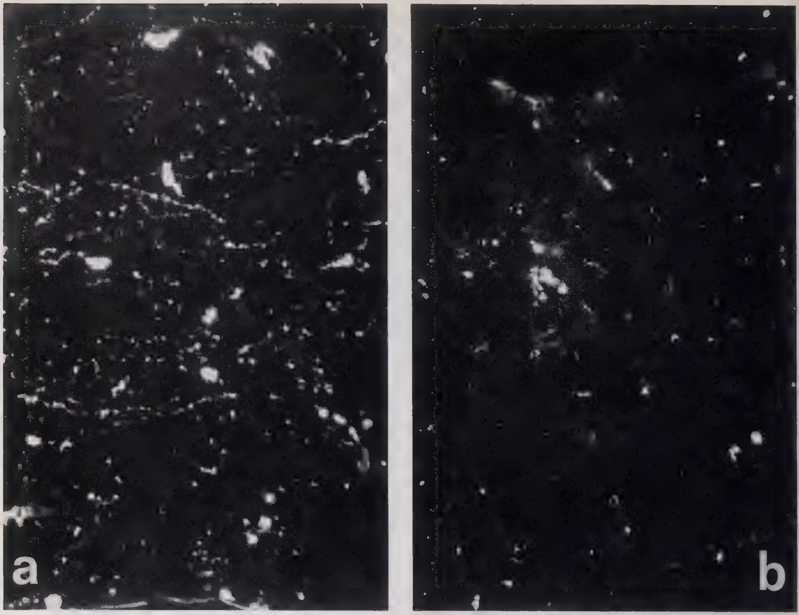

Fig. 4. Neuropeptide Y (NPY) of temporal cortex and in Alzheimer's disease (AD). **a:** control; **b:** AD. Decrease of density of NPY axonal varicosities and of intensity of their NPY immunological reaction. (Coon's method, fluorescence microscopy, ×570).

Neuropeptide Y (NPY). The NPY distribution in the human brain is comparable to the SOM distribution (57). In 80% of cortical SOM neurons there is also NPY (58).

Alzheimer's Disease. We observed in the cerebral cortex a loss of NPY neurons (some remaining NPY neurons are shrunken or contain NFT) and an important decrease of NPY axonal varicosities (Fig. 4b). In the PS, we found a store of NPY material (Fig. 5b) as observed by others (59, 60). The decrease of the amount of cortical NPY is equivalent to the decrease of SOM (61). In the substantia innominata, there is a significant increase of NPY (62); this increase reaches 80% (45) or 108% (22), similar to the increase of SOM.

Parkinson's Disease. Despite a marked reduction in the SOM concentration in the PD dementia cases, no significant change of NPY was found in cortex and hippocampus (27, 63).

Vasopressin (VP). In the neocortex, only VP fibers but no cell bodies were found (64–66). Some neocortical VP fibers originate probably in the locus coeruleus where VP is colocalized with NA in some perikarya (67). VP fibers in the hippocampus originate probably in the medial amygdaloid nucleus which projects to the subiculum (68). The subiculum is the area richest in VP receptors (69). VP has an excitatory role on hippocampal neurons (70) and enhances memory (71–74).

Alzheimer's Disease. VP decreases in the locus coeruleus lightly increases in the neocortex probably due to the cortical shrinkage and decreases significantly in hippocampus and in the accumbens nuclei (76, 77). VP decreases also in the CSF (78–80). The decrease of the hippocampic VP in AD should be related to the biochemical mechanisms of the dysmnesia. Treatment of AD with VP analogues resulted in some improvement of dementia (81, 82).

Parkinson's Disease. Extrahypothalamic VP is unchanged (25, 83).

Vasoactive Intestinal Peptide (VIP). In the human brain we observed morphologically that VIP is largely distributed in the neocortex, hippocampus, limbic cortex, amygdaloid complex,

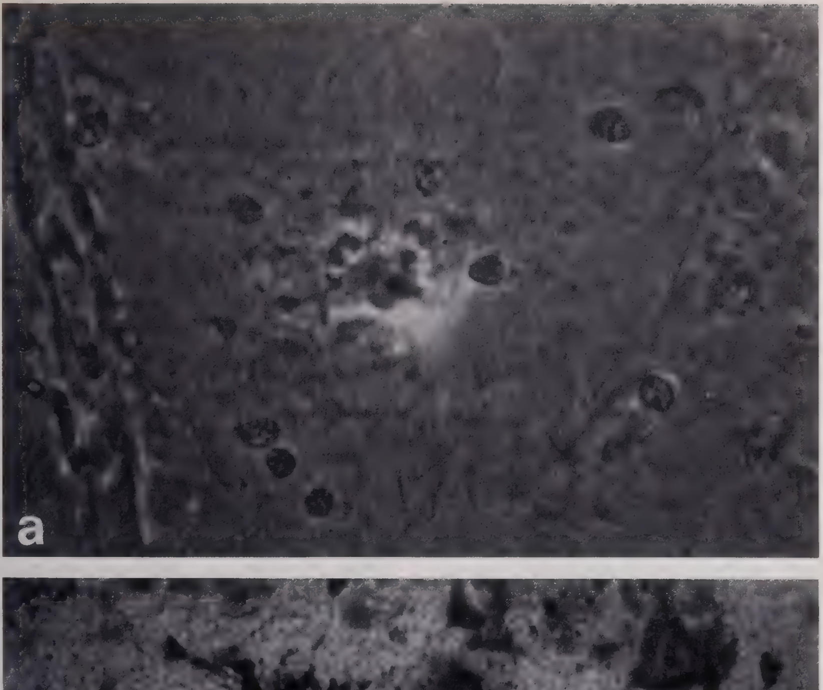

Fig. 5. Storage of neuropeptides inside or around senile plaques (PS). **a:** somatostatin; **b:** neuropeptide Y. Storage of neuropeptide (central light spot) is probably located above axonal lesion by PS inducing interruption of axonal neuropeptidic flow. (Coon's method, fluorescence microscopy, ×570.)

hypothalamus (14, 84); its level is high in CSF (85). VIP is colocalized with ACh in new cortical neurons (86).

Alzheimer's Disease. VIP is decreased significantly in insula and cingular cortex (44). Other studies have not found change in the cortex (87), septum (22) or CSF (88).

Parkinson's Disease. The VIP level is unchanged in the frontal cortex. There is no difference between PD with or without dementia (89).

Cholecystokinin (CCK-8). We have observed morphologically that CCK-8 is largely distributed in human brain (14, 90). CCK-8 is colocalized with DA in ventral midbrain A10 neurons which project to the nucleus accumbens and frontal cortex (91).

Alzheimer's Disease. CCK-8 is unchanged in the cortex (22, 92, 93) or lightly reduced (87). Administration of CCK-8 to patients with AD did not improve mental functions (94).

Parkinson's Disease. CCK-8 content is significantly reduced in the substantia nigra, but unchanged in other structures as caudate, putamen, pallidum, accumbens, frontal cortex, hypothalamus and ventral tegmental area (95, 96). The 40% reduction of CCK-8 level in substantia nigra probably results from the degeneration of CCK-8 containing neurons or interneurons, but not dopamine-CCK-8 neurons. CCK-8 has an excitatory effect on dopaminergic neurons in the substantia nigra in the rat (97). The nigric CCK-8 modulates the activity of nigrostriatal dopaminergic cells and deficiency may affect the expression of motor symptoms in PD.

Neurotensine (NT). Some bulky cell bodies in the subiculum projecting to the fimbria, fornix, septum, and mammillary bodies (components of the memory circuit of Papez) contain NY indicating a possible role on memory processing (98). NT perikarya are also observed in the amygdaloid nuclear complex. The medial septal nucleus, stria terminalis, caudate, and putamen contain NT axons and terminals. In the cortex, NT axons arising from the thalamus are observed, especially in the second cortical layer (99, 100).

Alzheimer's Disease. NT is unchanged in the cortex (43, 101) and decreased (−50%) in the septum (22).

Parkinson's Disease. NT is unchanged in pallidum, substantia nigra, putamen, and neocortex (27) and decreased in hippocampus (102). A considerable loss of high affinity NT receptors occurs on DA-cell bodies in the substantia nigra (103).

Enkephalin (ENK) and Endorphin (END). We realized in the human brain the morphological mapping of ENK (Met- and Leu-) axons and terminals (104). There is a parallelism between the localization of ENK and SP: (a) in the somatosensory systems of the spinal cord and in the brain stem (nociceptive antagonist); (b) ENK axonal terminals (from ENK-neuronal bodies in the striatum) reach the substantia nigra forming perisomatic contacts, and the pallidum forming peridendritic "pipe-shaped" structures (extrapyramidal regulations); (c) ENK-axonal terminals are observed in lateral septal, accumbens and interpeduncular nuclei, substantia innominata, hypothalamus, and cerebral cortex.

Alzheimer's Disease. Met-ENK is unchanged (105). β-END is decreased in CSF (106, 107). Treatment of AD with a Naloxone analogue resulted in some improvement of dementia (108).

Parkinson's Disease. Met-ENK is reduced by 70% in the substantia nigra compacta and ventral tegmental area or by 50% in the putamen and pallidum (19, 109, 110) and unchanged in the caudate, accumbens, globus pallidus interna, and other forebrain areas. In contrast, Leu-ENK is normal in substantia nigra, reduced in putamen and pallidum (109), and unchanged in cortex and hypothalamus (24).

In CSF of patients with advanced PD, Met-ENK and β-END-levels are unchanged (111, 112).

Adrenocorticotropin hormone (ACTH). Alzheimer's Disease. There is a significant decrease of ACTH in CSF that may reflect a decrease of cerebral ACTH (113). This decrease may explain the decrease of 17-cetosteroids and corticosteroids in AD (114). Probably the decrease of cerebral ACTH is implicated in biochemical mechanisms of the mnesic dysfunction. Treatment of AD with an ACTH analogue resulted in some improvement of dementia (115, 116).

Parkinson's Disease. ACTH is unchanged in hypothalamus (27, 117) and in CSF (118).

Corticotropin-Releasing Factor (CRF). The human brain contains CRF particularly in the hypothalamus and frontal cortex. CRF is found in lighter concentrations in amygdaloid nuclei, substantia innominata, temporal and parietal cortex, and caudate nucleus. Scarce CRF fibers are observed in posterior hippocampus and in accumbens nucleus (119).

Alzheimer's Disease. CRF decreases in the temporal and frontal cortex (−50%) and in the caudate nucleus (−70%) (119). The decrease is more important in the occipital cortex (−80%) with parallel increase of CRF receptors (120).

In Alzheimer's disease, CRF is reduced in CSF (121, 122).

Parkinson's Disease. Hypothalamic CRF content is unchanged (123).

Discussion

In AD, changes of neuropeptides are (a) hippocampus and neocortex: important decrease of SP, SOM, NPY, CRF; slight decrease of VP, CCK-8, VIP; (b) CSF: decrease of SP, SOM, VP, β-END, ACTH, CRF. These changes indicate a cortical hypoactivity of these neuropeptides due to the cortical lesions of cell bodies and axons. (c) Increase of SOM and NPY in the substantia innominata-BNM and of SP in the globus pallidus and substantia nigra.

In PD, SP, Met-ENK and CCK-8 decrease in the substantia nigra and globus pallidus. SOM decreases in frontal cortex and in hippocampus of demented cases. NT decreases in hippocampus. For other peptides, NPY, VP, ACTH, CRF, and VIP there are no significant changes.

Senile plaques (PS) and cortical peptides in AD: In AD the decrease of some cortical neurotransmitters may be induced by the PS; lesions of axons (ACh, NA, GABA, SOM, NPY, SP) implicated in PS may interupt the axonal flow and induce storage of neurotransmitters and related enzymes above the axonal injury, inside or around the PS. Storage of ACh or related enzymes CAT and AChE (124), NA (125), GAD (126), SOM (104, 127, 128) (Fig. 5a), NPV (60, 61, Fig. 5b), SP (16). These axonal lesions contribute to the decrease of the neurotransmitters in the cortex and in the CSF.

The cortical lesions of cholinergic and noradrenergic neurons by PS probably induce retrograde effects on their own cell bodies (ACh-neurons in the BNM, NA neurons in the locus coeruleus). The ACh neuronal loss in the different areas of the BNM is proportional to the density of PS in the cortical related areas (129), cortical lesions of different nature induce also a retrograde degeneration of ACh neurons in the BNM (130, 131).

Neurofibrillary tangles (NFT) and cortical peptides in AD: In AD, the decrease of some neurotransmitters may also be induced by NFT and the related neuronal loss. NFT in cortical glutamatergic cell bodies are probably related to the decrease of cortical glutamate and of the hypoactivity of the corticostriatal glutamatergic pathway. NFT in peptidergic cell bodies (SP, SOM, NPY) in the hippocampus and neocortex and the related loss of neurons and terminals may contribute to the decrease of the amount of these peptides.

Correlations between changes of peptides and changes of other neurotransmitter systems in AD and PD: The reciprocal relationships between perturbances of different neurotransmitter systems in AD and PD are difficult to establish, even for an heuristic hypothesis. To illustrate these difficulties, we discuss some hypothetical relationships.

Hypothetical relationships between SOM decrease in the cortex and cholinergic hypoactivity of the BNM in AD: In the cerebral cortex, there is (a) decrease of ACh and CAT and of the density of axonal cholinergic terminals arising from the BNM; (b) decrease of SOM cell bodies and their axonal terminals (Fig. 3b). In the BNM, there is (a) decrease of ACh neurons and of CAT; (b) increase of the density of SOM terminals and of their SOM-content (Fig. 3d).

We can exclude the reduction of the cortical SOM as the result of the basocortical cholinergic deficit, because the experimental lesions of the BNM that decrease the cortical CAT are without effect on the cortical SOM (132, 133).

In some cortical SOM neurons, there is AChE, indicating that these neurons receive cholinergic afferents (134, 135). It is possible that the primary cortical neuronal SOM loss induces a retrograde degeneration of ACh neurons in the BNM. There is a correlation between the decrease of cortical SOM and the CAT decrease (22, 42, 48). But the cortical neuronal SOM loss cannot be explain totally the ACh alterations of the BNM, except if these cholinergic neurons project exclusively on the cortical SOM neurons, which seems unlikely.

Hypothetical relationships between SOM increase in the BNM and cholinergic hypoactivity of this nucleus in AD: The SOM increase in the BNM could be apparent because of the atrophy of the nucleus. But we cannot exclude the possibility of a real increase of SOM in the BNM which should be primary in relation to the decrease of the ACh, which should be secondary. SOM activates cholinergic neurons in the BNM and increases the cortical release of ACh (35). Does the increase of the SOM in the BNM mean hypoactivity or hyperactivity of SOM at this level?

First hypothesis. The SOM increase in the BNM means SOM hypoactivity: reduction of the release and storage of the presynaptic SOM. As in BNM, SOM is excitatory. The decrease of the basocortical cholinergic activity should be the consequence of primary SOM hypoactivity. The SOM hypoactivity in the BNM could be due to an insufficient stimulation related to the deficiency of the cortico-subcortical excitatory glutamatergic pathways. So we can imagine the hypothetical chain of successive events: (a) PS and NFT in the cerebral cortex; lesions of glutamatergic neurons (excitatory) and deficiency of the cortico-subcortical glutamatergic pathways (136, 137) with increase of the Glu receptors in the striatum (138, 139). (b) Insufficient stimulation of subcortical SOM neurons whose axons reach the ACh-cell bodies in the BNM. (c) Decrease of the SOM release in the BNM (with presynaptic storage), insufficient stimulation of ACh neurons, and deficiency of the ACh-basocortical pathway. (d) Because the cholinergic basocortical hypoactivity, insufficient stimulation of cortical Glu neurons; in this way the vicious circle is closed with the tendency to self-maintaining.

Second hypothesis. The SOM increase in the BNM means SOM hyperactivity. In this case, the hypothetical chain may be the following: (a) primary cortical pathology (PS, NFT) and GABA and GAD deficiencies in cortex, caudate and thalamus (140–143). (b) the GABAergic hypoactive neurons inhibit not enough SOM neurons whose axons reach the BNM. SOM hyperactivity and excess of SOM in this nucleus. The thalamic and subcortical white matter neuronal populations containing simultaneously GABA and SOM (144, 145) could represent a relay of the GABAergic control on SOM in the BNM. (c) The primary SOM hyperactivity in the BNM could be excitotoxic on the basocortical cholinergic neurons with secondary cholinergic neuronal loss and (d) cholinergic basocortical deficiency. (In a similar manner may be discussed the increase of NPY in the BNM in AD).

Hypothetical relationships between changes of nigric SP in PD and AD and alterations of nigric DA and of other neurotransmitters: The axons of SP cell bodies located in the striatum terminate in the substantia nigra making excitatory synapses with DA and Gly neurons.

In Huntington's chorea, there is a primary destruction of SP-cell bodies in the striatum inducing a decrease of SP in the nigric axonal terminals (29, 30), that means SP hypoactivity at this level; inhibitory Gly interneurons are not sufficiently stimulated, resulting in Gly hypoactivity and increase of Gly receptors in the substantia nigra (146). GABA neurons in the striatum are also primarily altered with a consecutive striatonigric GABAergic hypoactivity.

The decrease of inhibitory inputs (GABA, Gly) on the nigric DA neurons is probably more important than the decrease of excitatory inputs (SP) inducing hyperactivity of the nigrostriatal DA pathway which is characteristic of Huntington's disease.

In PD, SP is also reduced in striatonigric axonal terminals (Fig. 2c) without injury of striatal SP-cell bodies. What does this decrease of nigric SP mean?

First hypothesis. The observed decrease of SP is due to an excess of the synaptic SP release, that means SP hyperactivity. The hypothetical chain of events could be the following: (a) Primary injury of DA neurons in the substantia nigra and deficiency of the inhibitory nigrostriatal DA pathway. (b) Insufficient inhibition of the striatal SP neurons and hyperactivity of the excitatory SP-striatonigric pathway. (c) Increase of the release of nigric SP and reduction of nigric SP. (d) The hyperstimulation of the DA neurons by SP could be toxic (the excitotoxic striatonigric SP hyperactivity may be primary and the lesion of DA neurons in the substantia nigra secondary). (e) Because the DA hypoactivity, the Gly interneurons are not sufficiently inhibited, let GLY-hyperactivity and GLY-receptors decrease (146).

Second hypothesis. The decrease of nigric SP means SP hypoactivity. The hypothetical chain of events could be the following: (a) DA hypoactivity in the substantia nigra. (b) Insufficient inhibition and hyperactivity of Gly interneurons and Gly receptors increase. (c) The Gly hyperactivity induces surinhibition of nigric SP. (d) Because of SP hypoactivity, insufficient stimulation of nigric DA neurons. (The nigric SP hypoactivity may be primary and the DA deficiency secondary.)

Third hypothesis. DA neurons in the substantia nigra receive SP input (excitatory), CCK-8 input (excitatory), ENK input (inhibitory). Normal coordinated activity of these nigric peptides is probably related to normal nigric DA activity. The decrease of SP, CCK-8, and ENK in the substantia nigra in PD may be the reflection of DA deficiency or a primary trouble inducing nigra DA deficiency.

In AD, nigric SP increases (Fig. 2b).

First hypothesis. The increase of nigric SP means SP hypoactivity with decrease of the release and presynaptic storage. Events could be the following: (a) Primary cortical lesion: PS and NFT in Glu-cell bodies. (b) Deficiency of the excitatory corticostriatal Glu pathway. (c) Insufficient stimulation of the SP neurons in the striatum, hypoactivity of the striatonigric SP pathway; decrease of the SP release and presynaptic storage. (d) DA neurons in the substantia nigra are not sufficiently stimulated, that induces a nigrostriatal DA decrease and a slight extrapyramidal syndrome.

Second hypothesis. The increase of nigric SP means SP-hyperactivity. (a) Primary cortical lesion and deficiency of the excitatory corticostriatal Glu-pathway. (b) The inhibitory GABAergic neurons in the striatum are not sufficiently stimulated, that induces GABAergic hypoactivity. (c) The GABAergic neurons inhibit not sufficiently the striatonigric SP pathway which becomes hyperactive and enhances the nigric SP activity. (d) The nigric hyperactive SP is excitotoxic on DA neurons (or hyperstimulates the inhibitory Gly interneurons). The consequences: injury or suprainhibition of DA neurons, nigrostriatal DA deficiency, and slight extrapyramidal syndrome.

Summary

In Alzheimer's disease, the most important changes of neuropeptides are (a) in the hippocampus and neocortex: decrease of SOM, NPY, SP, CRF, VP, CCK-8, and VIP; (b) in the basal nucleus of Meynert (BNM), increase of SOM and NPY; (c) in the substantia nigra and globus pallidus, increase of SP.

The decrease of cortical neuropeptides may be induced by the primary cortical injury: senile plaques (PS) and neurofibrillary tangles (NFT).

The increase of SOM in the BNM may be primary (in relation to the cortical pathology via Glu and GABA deficiencies) and may induce secondarily alterations of the ACh neurons of the BNM and contribute to the hypoactivity of the basocortical ACh pathway. The increase of the nigric SP may be also of the reflection of cortical pathology and may induce slight DA deficiency.

In Parkinson's disease the most important changes of neuropeptides are (a) in substantia nigra and globus pallidus, decrease of SP, Met-ENK and CCK-8; (b) in hippocampus and neocortex, decrease of SOM and NT. The decrease of cortical SOM is related to the associated dementia. The decrease of neuropeptides in the pallidum and substantia nigra in PD may be (a) induced by the DA deficiency or (b) primary inducing secondarily the DA deficiency.

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ANNOUNCING

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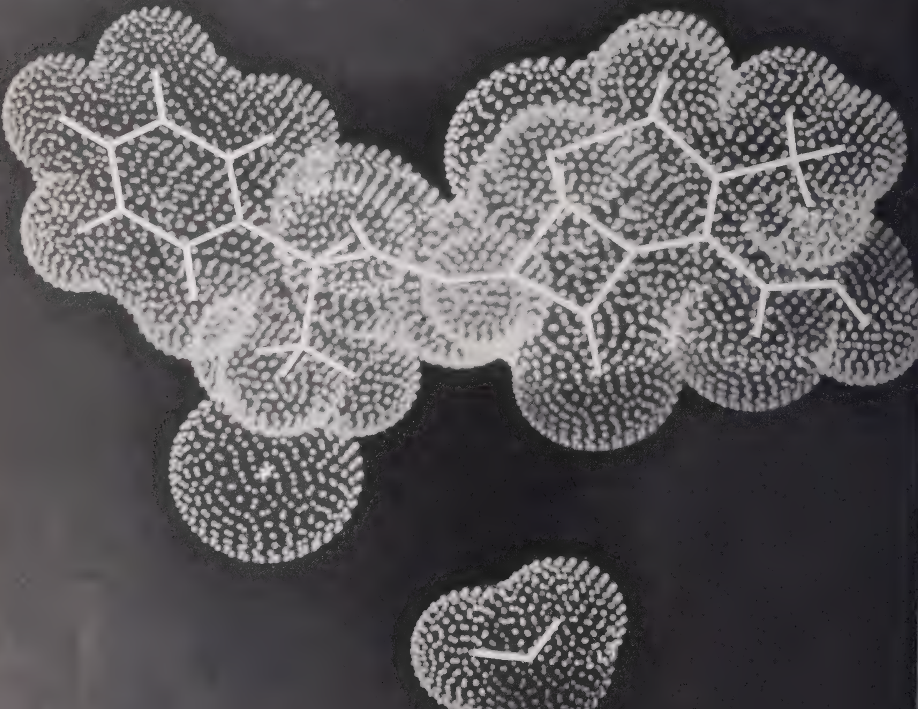

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usceptible strains of *Staphylococcus aureus* and/or β-hemolytic streptococci.
usceptible strains of *Escherichia coli, Proteus mirabilis,* and *Klebsiella* sp.
usceptible strains of group A β-hemolytic streptococci.

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(cephalexin hydrochloride monohydrate)

Summary: Consult the package literature for prescribing information.

Indications and Usage:

Respiratory tract infections caused by susceptible strains of *Streptococcus pneumoniae* and group A β-hemolytic streptococci.

Skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* and/or β-hemolytic streptococci.

Bone infections caused by susceptible strains of *S aureus* and/or *Proteus mirabilis.*

Genitourinary tract infections, including acute prostatitis, caused by susceptible strains of *Escherichia coli, P mirabilis,* and *Klebsiella* sp.

Contraindication: Known allergy to cephalosporins.

Warnings: KEFTAB SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:

- Discontinue Keftab in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Keftab should be administered cautiously in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy and lactation. Cephalexin is excreted in mother's milk. Exercise caution in prescribing Keftab for these patients.
- Safety and effectiveness in children have not been established.

Adverse Reactions:

- *Gastrointestinal,* including diarrhea and, rarely, nausea and vomiting. Transient hepatitis and cholestatic jaundice have been reported rarely.
- *Hypersensitivity* in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis.
- *Anaphylaxis* has been reported.
- *Other reactions* have included genital/anal pruritus, genital moniliasis, vaginitis/vaginal discharge, dizziness, fatigue, headache, eosinophilia, neutropenia, and thrombocytopenia; reversible interstitial nephritis has been reported rarely.
- Cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment.
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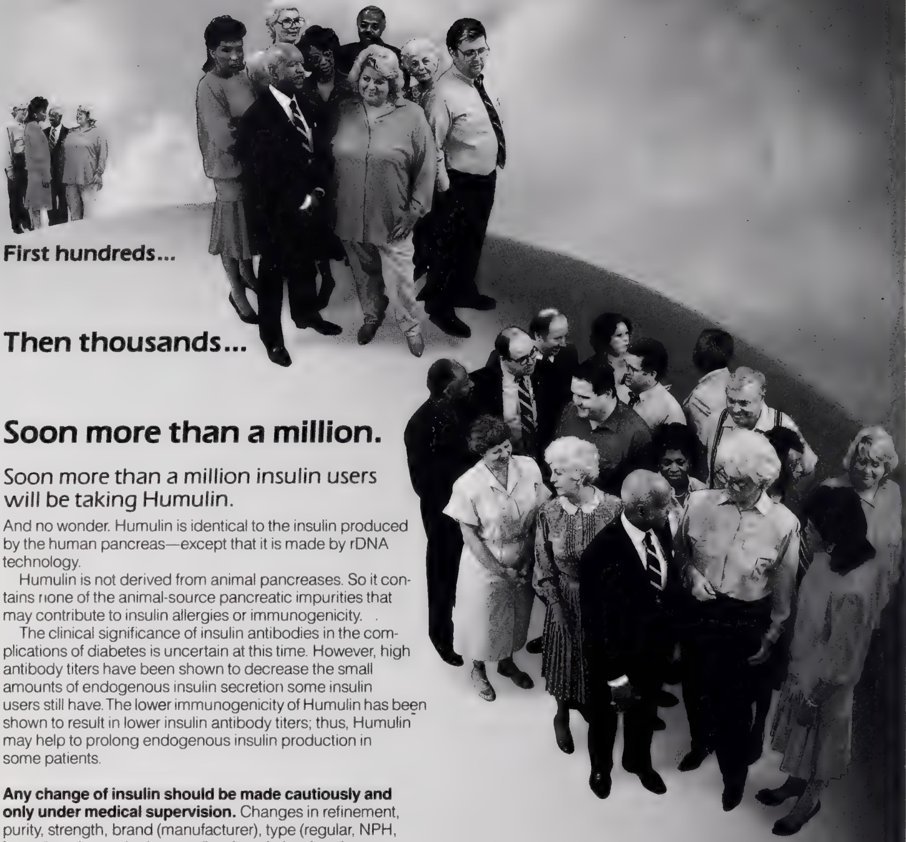

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HMOs: An Answer to Fee-for-Service?

NANCY ARIES, PHD, AND MARIANNE C. FAHS, PHD, MPH

Abstract

We examine the incentives and disincentives of fee-for-service medicine and the options for reform which will assure cost efficiency and quality of care. We find fee-for-service an inflationary system that implicitly encourages physicians to disaggregate services, increase charges, and practice more costly forms of medicine. Reform options include the modification of physician practice, the revision of reimbursement methods to eliminate existing disparities, and the substitution of capitation for fee-for-service. Particular attention is paid to the trade-offs between the incentives to over- or under-use services under fee-for-service and capitated systems, including for-profit and nonprofit HMOs. The issue of reimbursement is tied to broader policy debates on regulation versus competition.

The organization and financing of medical services is undergoing rapid change. The number of health maintenance organizations (HMOs) increased from 178 plans, with an enrollment of 5.7 million in 1977, to 400 plans with an estimated 19 million subscribers in 1985 (1). Market penetration of HMOs is estimated to rise from the current 9% to 30% in the next decade. Other systems of health care delivery are also proliferating: preferred provider organizations (PPOs), health care corporations, and independent practice associations (IPAs). If current trends continue, 90% of physicians will be working in managed care systems by the year 2000.

Reorganization of the financing system has a singular goal: control of health care costs. In the last twenty years, the cost of health care has risen faster than costs associated with other sectors of the economy (2). Thus the provision of health services is consuming an increasing proportion of every dollar spent. In 1960, health care expenditures accounted for 5.3% of the GNP. That figure has now doubled (3). Because of extreme inflation in health care costs, most consumers face increasing health costs, benefit reductions, or access barriers. The elderly, for example, now pay a larger portion of their income for health care than they did before Medicare was enacted (4).

Historical Background. Historically, the health care system has been organized around independent practitioners who provided individualized services and were paid on a fee-for-service basis. The economic incentives of this form of independent, fee-for-service practice were toward a costly and inflationary system (5, 6). Proponents of change argue that by altering the payment structure, incentives can be altered to jointly reduce the total growth of health care costs and reallocate health care resources to more efficient and effective uses (7).

To date, most cost containment efforts have been directed at hospitals, because the major portion of medical care charges are incurred during the provision of inpatient care (8). It is physicians, however, who direct over 80% of medical care expenditures, through their decisions regarding diagnostic studies, treatment, and hospital admissions (9). To be effective, cost containment efforts must involve the delivery and reimbursement of physician services (6, 10).

Therefore, this paper examines reimburse-

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ment of physicians: how charges are generated under fee-for-service practice; the incentives and disincentives in the existing reimbursement system; and the possibilities for reform to encourage the practice of high-quality medicine in a cost-effective manner. More specifically, this paper assesses systems of capitation payment as an alternative to fee-for-service medicine and the tradeoffs incurred in the delivery of health services.

Fee-for-Service

Fee-for-service refers to the method by which physicians charge patients for services rendered. Initially, fee-for-service was a flexible reimbursement system (11). Physicians determined the appropriate mix of services and the price for each service. Thus they had the ability to vary charges depending on criteria such as patients' ability to pay, or the varying cost of inputs (12–14).

Fee-for-service has lost its flexibility because today more than 80% of the population has some form of health insurance (8). Third-party reimbursement requires that fees be standardized among providers. This can be accomplished through the use of fee schedules or a method of reimbursement referred to as customary, prevailing, and reasonable charge (CPR).

Medicaid, the public insurance program for the poor, uses a fee schedule. The Medicaid program publishes a list of maximum allowances for each service. Physicians are then reimbursed whichever is less, their charge or the maximum allowance set by Medicaid.

By contrast, the CPR method, used by Medicare and similarly by most private insurors, approves physicians' charges based on four fee screens. The approved charge is the lowest of (a) the customary charge for that physician (defined as the physician's median charge for the procedure during the previous year); (b) the prevailing charge in that region for a similar service (defined as the 75th percentile of the customary charge of all physicians in the area, weighted by the number of times each physician performed the service); (c) the physician's actual charge; and (d) the private business charge for a comparable service (15).

Not only is the CPR method of reimbursement rigid; it is also confusing to both beneficiaries and physicians (16). Typically, neither party knows in advance how much the patient's particular insuror will allow. In addition, there is the awkward question of assignment and the uncertainty in prices which it generates. Physicians who accept assignment may not know how much to bill patients because the rate of reimbursement may be unknown. On nonassigned claims, physicians face the possibility of nonpayment. Beneficiaries also face uncertain prices. On assigned claims, their liability is a percentage of covered and approved charges. On nonassigned claims, their liability is the difference between the physician's charge and the approved third-party payment in addition to a percentage of approved charges. In either case, a disproportionate financial burden is placed on the poor, the sick, and the elderly (4).

Structural Biases of Reimbursement Incentives. Current methods for paying physicians have a number of drawbacks that contribute to escalating costs. Generally, fee-for-service medicine is considered inflationary because it is a cost-based method of reimbursement (17). Physicians are reimbursed for each additional unit of service rendered. Therefore, physicians have a built-in incentive to provide more rather than fewer services. Between 1975 and 1982, roughly 34% of the annual rate of growth in Medicare payments to physicians was explained by increased number of services per enrollee (18). However, the extent to which this increase was due to patients' increasing demands or needs cannot be determined from the data.

Second, the fee-for-service system implicitly encourages physicians to increase charges (17, 19). Under the CPR charge method, current levels of reimbursement are based on the previous year's charges. Thus the system has allowed fees to escalate dramatically. Since 1975, the inflation rate for physician charges under the Medicare program has been higher than increases in the Consumer Price Index (CPI); in the early 1980s, it grew 50% faster than did general inflation (20).

There is also the question of whether CPR-determined fees are "sticky downwards" (17). According to economic theory, prices should fall as production achieves greater efficiency. This has not been the case in medicine; fees do not decline as increased physician proficiency reduces the cost of procedures. One example is coronary-artery bypass surgery (21). Initial payment recognized the surgeon's exceptional time commitment—as much as 20 hours per patient of direct involvement in diagnostic studies, preoperative preparation, surgery, and personal supervision of postoperative care. The procedure now requires 2 to 4 hours of the surgeon's time, and ancillary care can be delegated to residents and other health providers. The surgeon's fee, however, has not been adjusted downward.

Third, since payment is based on customary and prevailing charges, the method has tended to freeze in place historic disparities in the fees charged by physicians (4, 22). Specialists and surgeons, traditionally paid more for their services, are compensated far more for relatively brief and simple procedures than are primary care physicians for time-consuming diagnoses and counseling. One study found that specialists received 19% to 53% more for the five most common types of office and hospital visits, after explicitly accounting for differences in medical training, costs, overhead, complexity, and patient time spent (23). Although the rate of reimbursement varied, there was no evidence that the visits required the specialists' expertise. The system has spurred growth in the number of specialists and surgeons, and encouraged other physicians to provide costly services that specialists and surgeons customarily dispense.

Finally, reimbursement disparities relate to practice location (4, 22). The fee-for-service system has a built-in bias toward hospital-based practice and urban rather than rural location. Physicians are paid 4 to 5 times as much per hour for procedures performed on an inpatient basis (24). The same physician can earn 2 times more per hour for hospital visits than for office visits (25). Furthermore, in metropolitan areas, physician charges are 23% higher on average than in nonmetropolitan areas, and this geographic–demographic difference has progressively widened (26). By allowing charge differences greater than can be accounted for by differences in cost of living and professional expenses, reimbursement systems like Medicare provide an incentive for physicians to locate in areas where reimbursement is higher.

Practice Incentive. The economic pressure to constantly provide more services at a higher cost points to the issue of physician practice. As noted above, the financial incentives of the maximum fee schedule and CPR charge system support technologically intensive care, as opposed to consultative and preventive services (27). In a study which modeled the practices of 5 internists, it was found that physicians could increase their net incomes by a factor of 3 if their service mix was changed from one which emphasized cognitive medicine to one which favored office procedures and testing (28).

The cost of new medical technology would not be under such scrutiny if the clinical effectiveness was not being questioned. Physicians' use of laboratory tests varies widely without any evidence that the variation is related to improved patient outcome. One study suggests that laboratory tests in a teaching hospital could be cut 47% without any apparent loss in the quality of patient care (29). Another study claims that only 5% of laboratory chemistry tests affect the clinical decisions for hospitalized patients (30). As in most areas of medicine, the gray area is quite large (5). Although physicians would agree that there is waste in the system, there is no consensus on what constitutes optimal testing.

Future Options for Payment of Physicians

Given the complexity of the reimbursement system and the relation of that system to the cost of care, it is not surprising that there are as many options for reform as there are policy-makers. The overall intent of these proposals, however, is to reduce the level of spending and the speed at which spending increases. The various proposals can be categorized by the extent to which they will reform the organization and financing of the health care system.

Modifying Physicians' Practice

Reeducating Physicians. The first set of proposals disregards the method of reimbursement and focuses attention on how physicians practice medicine. Such strategies primarily involve educational programs and monitoring of physician practice. The goals are to increase physicians' knowledge of the clinical utility of available tests and procedures and to standardize their practice.

In the area of laboratory testing, for example, emphasis is placed on teaching physicians about the selectivity, sensitivity, and predictive value of tests (31). Such education is seen as a means of upgrading clinical practice and controlling unnecessary costs. Some hospitals have begun comparing physicians' ordering behavior to that of other physicians and to departmental protocols. The intent is to modify the behavior of those physicians whose practice does not conform to the norm.

Although it is important that physician practice be effective in terms of both outcome and cost, the shortcoming of educational strategies is that they can only contain marginal costs. The cost of excess service, however, is relatively small when compared to the overall cost of the health care system. In a two-year program to test physician education as a strategy to reduce hospital costs, it was found that the decrease of selected ancillary services did not have a significant impact on total hospital charges (32). A second criticism is that educational strategies do not address the disparities in the fee-for-service practice. The incentives still remain to provide technological care in major medical centers. Thus physicians will find themselves walking a thin line between quality and cost effectiveness. Finally, cost-awareness educational programs, when used alone, have had mixed results in assuring appropriate reductions in test utilization (33).

Increasing Cost-Sharing by Patients. A second strategy to modify physician practice has been directed at the patient. This strategy calls for increased cost-sharing by the patient, that is, increased out-of-pocket expenditures by the patient for medical care. The rationale behind this approach is that physicians will respond to the patient's heightened awareness of the cost of treatment by reducing diagnostic and treatment inefficiencies. Research suggests that cost-sharing does reduce utilization (34). However, when physician response to increased cost-sharing for a large group of patients was studied, the opposite effect occurred (35). Physicians were found to cost-shift, that is, to increase ambulatory charges and hospital use for the remaining patients in the practice. Indeed, increased cost-sharing among Medicare patients has done little to restrain costs. Thus the efficacy of patient cost-sharing as a cost containment strategy is doubtful.

Reforming Fee-for-Service Reimbursement

There is general agreement that strategies to modify physician practice to induce greater cost-consciousness have limited effectiveness. Therefore, strategies to control physician costs must also be directed at the reimbursement system. Reform strategies take fee-for-service as the basic mode of reimbursement but seek to eliminate the disparities in the system and perhaps also to reshape the incentives.

Competition among Providers: PPOs. One set of proposals attempts to foster greater competition among health care providers. An increasingly popular arrangement is the preferred provider organization (PPO). The reported number of operational PPOs as of June 1, 1985 was 229, with a subscriber population of roughly 10 million (36). The PPO is a contractual arrangement between a group of providers, including physicians and hospitals, and a purchaser of health care services. The providers agree to discount their fees for patients covered under this agreement.

A competitive arrangement such as a PPO, however, offers only a partial solution to the problem of health care costs (37). The PPO can effectively control costs for a group of patients and third-party payers, but its attraction remains limited to areas in which physicians are already competing for patients. Further, PPOs do not address inequities in the system as a whole. They represent, in effect, only a wage cut for participating physicians and do not address the disparity in the way fee-for-service is determined or the ways it may influence physicians' patterns of practice.

Reimbursement by Relative Value Scale. A second reform strategy is to eliminate the disparities that exist in the CPR system through the use of a relative value scale (RVS) (24). This reimbursement method was first developed by the California Medical Association (38). A relative value scale ranks each physician service or procedure in order of value. Value is based on such factors as difficulty, risk, resources used, and time required to provide services. Once developed, the value scale can be converted into a fee schedule by assigning a dollar amount to the RVS unit.

Relative value scales can eliminate the methodologic inequities in the current fee-for-service system by eliminating unjustifiable differentials between urban and rural locations, specialization and nonspecialization of providers, and technological and cognitive care. RVSs, however, still retain the practice-related incentives of fee-for-service reimbursement. Physicians who overprovide services or disaggregate services into a greater number of billable tasks still benefit economically.

Redefining Unit of Service: Payment by Case. A third reform strategy calls for physician diagnosis related groups (DRGs) (39). Such a payment method would retain the concept of fee-for-service but redefine the unit of service. Rather than reimbursing physicians on a procedure-by-procedure basis, a flat payment would be made for each case. Physician DRGs are thus a method of bundling the costs of physician services. The incentives of physician DRGs stand in sharp contrast to those of the CPR charge system. Physicians who provide less service would be in a position to maximize revenue.

Physician DRGs carry with them strengths and weaknesses similar to the hospital DRGs (40, 41). First, physicians may possibly provide less than the optimal quantity of services in order to keep costs within a set level of reimbursement. Similarly, there is a potential for underuse of needed expensive services or denial of care to very ill and potentially resource-intensive patients.

A second area of concern is the problem of determining the diagnostic groups. A simulation of the potential impact of physician DRGs showed that there is little variation between patients in the cost of surgical problems (39). Surgical DRGs, therefore, could be equitably implemented. But medical DRGs could not be; patient costs are far less homogeneous. The exceedingly difficult task of defining separable episodes of ambulatory treatment, not to mention the problems of multiple diagnoses and levels of severity, may preclude using this method of payment as a realistic strategy.

Alternatives to Fee-for-Service

A final possibility is to consider the alternatives to fee-for-service reimbursement of physicians. Such a suggestion is not altogether unreasonable. With the changing organizational basis of health delivery, increasing numbers of physicians are being paid on an hourly basis (23). Group practices now include over 51% of office-based physicians. Fifty-two percent of group practice physicians receive salaries. Similarly, 26% of physicians have financial arrangements with hospitals which provide 62% of net practice income. Payment to 59% of these physicians is based on salary. Thus the dominance of the fee-for-service system as a method of direct payment to physicians is already eroding.

Capitation. The most obvious reimbursement alternative to fee-for-service is some system of capitation. The concept of capitation has three important elements (42).

- First, the enrollee or beneficiary is the unit of payment. Physicians or groups of physicians receive a fixed payment for each patient or potential patient who enrolls, whether or not the patient uses any medical services during a given enrollment period, usually a year. Thus, revenue is increased by enrolling additional people into the plan.
- Second, the physician is responsible for providing the full range of services patients require. Remuneration does not depend on the services used. There is, therefore, no financial incentive to provide additional units of service to generate additional revenue. Patients, on the other hand, have access to comprehensive and continuous medical care.
- Third, payment is set in advance. This prospective aspect implies that the physician has a defined population for which he or she is responsible and a predictable budget within which to provide that care. Patients also have predictable monthly or yearly expenses, and the system does not penalize the sick.

At present capitation systems take two major organizational forms: independent practice associations (IPA), and prepaid group practices (PPGP). Both of these are considered health maintenance organizations (HMO).

Independent Practice Associations. Structurally, the IPA bears the closest resemblance to existing patterns of medical practice. Physicians who belong to an IPA continue to practice individually or in groups. IPA enrollees contact an IPA physician for services, and the physician bills the IPA on a fee-for-service basis. The difference between the IPA and the more traditional CPR system of reimbursement is that the IPA's group budget is constrained by the beneficiaries' capitation payments. Physicians as a group assume financial responsibility for the utilization of all services, both ambulatory and hospitalizations, which ultimately translates into their ability to provide services at competitive premiums with other fee-for-service insurors.

Prepaid Group Practices. Prepaid group practices take a different organizational form. Physicians do not retain independent practices. Physicians either work as staff members of the administering agency (staff model), or for a group practice which contracts with the administering agency (group model), or for one of several group practices which contract with the administering agency and thus form a network of providers (network model). Here also the patient who belongs to a PPGP pays a fixed payment per year and is guaranteed all covered services necessary for that time period.

HMOs and Profit-Making Status. A significant issue for HMOs today is the profit-making status of the organization (43). Most older PPGPs are not-for-profit. Examples of these HMOs include the Kaiser-Permanente Medical Care Program, found largely on the West Coast; the Group Health Cooperative of Puget Sound; Group Health Association, Inc., in Washington, D.C.; and the Health Insurance Plan of Greater New York (HIP). Physicians are salaried employees who bear limited direct financial risk for the cost of providing services. Although there is the possibility of an end-of-year bonus, there is minimal downside risk. By working for the PPGP, physicians insure themselves as a group against excessive financial burden.

Newer HMOs, both IPAs and PPGPs, are more often for-profit corporations; the Empire HMO of Blue Cross and Blue Shield and Maxicare are two examples. These organizations have chosen a model for paying physicians differing from the straight-salary or the salary-plus-productivity-incentives model. This system is known as risk-sharing. In a risk-sharing HMO, physicians directly share in the financial risk of high utilization and expenditures. There is typically a per-patient form of accounting, against which physicians draw as services are rendered. At the end of the fiscal year, patient accounts are balanced and physicians receive a portion of the difference between the capitation income and the sum drawn. These systems most often reimburse individual physicians for ambulatory services alone or on a prepaid basis under "managed care" arrangements.

Cost Reduction via Capitation. Reimbursement based on capitation has the proven ability to reduce costs. Studies demonstrate different patterns of utilization between HMOs and fee-for-service practices. Members of prepaid group practices have similar ambulatory visit rates per year and lower rates of hospital admissions than do users of fee-for-service medicine (44–46). Total expenditures in HMOs have deen documented to be 10% to 40% lower than in solo fee-for-service practices (42). This difference has been achieved by decreasing the rate of hospital admissions and then only among those HMOs owning their own hospitals. HMOs have not, however, been shown to affect the trend in the rate of growth of expenditures (47).

Skeptics who challenge these cost savings have argued that the difference can be attributed to the fact that the population in HMOs is generally healthier than the population in fee-for-service practices (48). To test this hypothesis, a controlled trial was run in which a population sample was randomly assigned to an HMO or to fee-for-service physicians (49). In this trial of the effect of an HMO on medical care expenditures, the HMO was found to reduce expenditures by 25% compared with fee-for-service medicine. This was due entirely to a 40% reduction in the rate of hospital admissions.

Critics of HMOs have also argued that organizational factors other than method of payment are responsible for the difference in practice costs (50). For instance, many comparisons have been made between organizations that differ in size. This factor of organization size is important because studies have shown that the use of ambulatory tests in large group practices may be twice as high as that in smaller groups (51). Yet in a recent study of ambulatory testing by internists, of patients with uncomplicated hypertension, fee-for-service physicians were found to order 50% more electrocardiograms and 40% more chest radiographs than not-for-profit HMO doctors (52). These results were obtained after controlling for group size and correcting for patients' age, sex, duration and severity of disease, as measured by pretreatment blood pressure, and the physician's year of medical school graduation.

Quality of Care in HMOs. As for quality, numerous studies indicate that quality of care is better, or at least no worse, in HMOs (53–55). Quality is extremely difficult to measure, given the number of possible indicators (56, 57). One set of criteria is structural, meaning the characteristics of providers. HMO physicians, for example, are more likely to be board certified than the average fee-for-service physician (58). But whether such a structural measure actually translates into better quality of care is an open question.

Another measure of quality is a process-oriented review of the actions taken in specific cases. This method emphasizes the record-keeping abilities of the provider. Superior performance among prepaid groups has been attributed to their ability to assure that each patient is treated by an appropriate specialist in a large hospital, thereby meeting standards for process of care (42).

Finally, outcome studies of quality focus on the end results of medical care, generally indicated by mortality and morbidity measures or by number of disability days. Available data suggest that HMO outcomes do not differ significantly from those of conventional practices (59).

Consumer Satisfaction. The measures of quality discussed above assess professional conduct. Consumer satisfaction is also a crucial indicator of performance (60). Overall, patients' evaluations of HMO quality may be somewhat more negative than evaluations of fee-for-service practices (42). Out-of-plan utilization and enrollment-disenrollment decisions have also been examined as correlates of satisfaction. If outside use represents dissatisfaction, then 5% to 10% of HMO members are dissatisfied (61). Some even "vote with their feet" and disenroll when the opportunity arises (62). Yet enrollment trends within the same employer groups show that HMOs tend to increase, not decrease, their market share (42).

Physician Satisfaction. Physician satisfaction, the final measure of quality, is not so much an indicator of success as a prerequisite to HMO development. Few HMO physicians are dissatisfied with their salaries from HMO practices (58). Indeed, stable and reduced hours are an advantage. However, dissatisfaction has been registered with the lack of incentives to expand hours and the overwhelming patient load as a consequence

(63). Physicians may not have enough time to devote to each patient, which can result in treating psychosocial problems symptomatically (42). Efforts to improve productivity can exacerbate the problem.

Quality of Care and Profit-Making. All the data on quality discussed above apply only to the older, not-for-profit HMOs. Although a for-profit HMO does not necessarily imply a difference in quality, there are differences in orientation that must be considered. James A. Vohs, chief executive officer of Kaiser Foundation Health Plan, has commented that the profit status of an organization is not the key variable in the determination of quality. Rather, it is the "motivating forces behind an organization and its values" (64). If an HMO sees itself as a short-run, windfall-profit-taking organization, quality is likely to suffer. If the organization is oriented toward the long term, quality is likely to be maintained.

This sounds plausible until we consider that even for-profit organizations oriented to the long term are geared to the short-term quarterly report. Stock prices rise and fall depending on quarterly reports. Practical short-term requirements to maintain or increase earnings may affect quality. One possible scenario is that patient access to high cost services will be limited during quarters with low enrollment expansion.

The concern is that physician practice in risk-sharing HMOs might err in the opposite direction from fee-for-service arrangements and encourage the withholding of services because of a lack of fiscal neutrality in the operational objectives, fiscal neutrality being the ability to minimize the conflict between the physician's financial interests and the patient's medical outcome (65). For this reason, nonprofits, in the past, have shied away from the risk-sharing form of physician payment. Where physicians are salaried and receive bonuses based on group performance, the incentive to underuse services is minimized. Although raises and bonuses depend on whether the group as a whole over- or under-utilizes services, the immediate risks and personal gains are dispersed. Thus the connection between practice and payment for the individual physician is modified.

Conclusions

Does the potential for physicians to underuse services in a competitive, for-profit environment outweigh the potential for physician excesses in a fee-for-service environment? That is an underlying question in current debates on physician reimbursement. The debate, however, has taken on strong ideological overtones. On the one hand, fee-for-service has been associated with the regulatory era of the 1970s, and capitation has been heralded as the harbinger of competition. On the other hand, fee-for-service has been associated with values such as physician autonomy and free enterprise, and capitation has been denounced as an omen of socialized medicine.

It is useful to separate rhetoric from reality. Fee-for-service, as it evolved under CPR, is indeed a semiregulated form of payment. Price regulation is advisable when market conditions result in a monopoly. Although not all economists agree on this point, many contend that physicians have monopoly power because they control not only entry into the profession, but also the information flow that is necessary to evaluate the need for and the value of their services. Since these aspects of the medical profession have been accepted by the public, semiregulated prices evolved.

Capitation is a payment strategy that includes the concepts of prepayment, planned program budgets, continuity, comprehensiveness, and responsibility for a defined population. There are many organizational modes within which capitation can be an appropriate system of payment. In fact, capitation is possible both in a regulated health care system and in a competitive, or market-oriented, health care system. The form in which capitated payment systems are now emerging wears the fashionable garb of the competitive marketplace. The for-profit HMO is an example of a competitive strategy designed to provide quality care in a cost-effective manner.

There is, however, one market prerequisite critical to the effectiveness of the competitive strategy. This prerequisite is consumer sovereignty, that is, the ability of consumers to be informed decision-makers. The presumption is that consumers will enter the medical marketplace with adequate information regarding the nature, quality, and cost of care. Consumers will then be able to make informed choices regarding alternate health care plans and the utilization of services within these plans. If this presumption fails to hold, further development of a regulated system may be necessary. For instance, publicly supported information collection and distribution is a form of regulation that might strengthen the market principles of competition.

Combining the best aspects of regulation and competition to form a mixed market system requires consummate skill. The crucial issue, then, for policy makers and physicians is to move beyond the ideological debates and look carefully at the comparable merits and problems of fee-for-service as distinct from capitation. A likely and promising outcome is a landscape characterized by many different organizational forms whose diversity may aid in consolidating a medical care system with appropriate checks and balances.

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The first part of this study was an analysis of the cholinergic, adrenergic, and peptidergic pathways. It discussed their positive and negative components. The second part, presented here, explores the integration of neural and hormonal mechanisms, an area intriguing physiologists and gastroenterologists since the original reports of Pavlov and Bayliss and Starling. It is most probable that both mechanisms are of major importance in human digestion, the hormonal representing the spigot of enzyme secretion and the neural acting as modulator, both positive and negative, to the enzyme responses of the pancreas to food intake.—David A. Dreiling

Neural Control of the Exocrine Pancreas:

An Analysis of the Cholinergic, Adrenergic, and Peptidergic Pathways and Their Positive and Negative Components

2. Integration of Neural and Hormonal Mechanisms

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It is generally believed that exocrine pancreatic secretion (EPS) is regulated mainly by hormonal mechanisms and that any effect of vagal cholinergic nerves on pancreatic secretion is due to indirect effects on hormone release rather than to direct effects on the pancreas. However, several studies support an important role for direct cholinergic regulation of both bicarbonate and enzyme secretion from pancreon units. Indeed, practically all studies indicate that vagotomy or atropine administration will depress pancreon enzyme secretion to intestinal stimuli. Three plausible explanations for these phenomena are that vagotomy or atropine (a) interferes with the effects of CCK on the acinar cells, (b) interferes with CCK release in the gastrointestinal mucosa, or (c) interrupts a vagal cholinergic reflex from the intestines to the pancreas, that is, short, medium, and long arc reflexes (147).

The first possibility has little support. In in vitro systems, atropine does not influence CCK effects on acinar cells. According to Solomon (147), those reports of an atropine-elicited enzymatic depression following CCK administration are erroneous and result from the administration of high doses of the muscarinic blocker, which evoke nonspecific collateral effects. Another factor leading to misinterpretation is that atropine depresses basal enzymatic secretion, which —if not related to poststimulation levels at low doses of CCK—would result in an erroneous impression of enzymatic depression. Thus, atropine lacks in vivo influence over the CCK-evoked enzymatic secretion. The same phenomena are observed after vagotomy.

The second possibility, that vagotomy or atropine interferes with CCK release from the intestine, seems to have been negated by the studies of Grossman et al (57–60). CCK blood concentrations were determined in rodents following subcutaneous autotransplantation of pancreatic segments, external secretion exteriorized

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through a nipple of the mammary gland. In these experiments, the EPS response of the autotransplanted pancreas to intestinal stimuli was diminished, an effect not augmented by vagotomy or atropine. Neither was the CCK-releasing capacity of the gut altered by vagotomy or atropine. These results suggest that extrinsic denervation of the autotransplanted pancreas induces decreased EPS response to intestinal stimuli. Other crucial experiments are those that compare the latency of the EPS response to intestinal stimuli and the intraportal injection of CCK. With intraduodenal infusion of tryptophane or sodium oleate, the EPS delay is about 25 sec, compared with intraportal CCK injection, in which the delay is about 40 sec. Atropine and vagotomy increase the latency of response to intraduodenal stimuli but do not modify the effect of intraportal CCK. All these studies indicate that the enteric signals to pancreon units and to the PP cells are mediated via a cholinergic pathway.

According to Grossman (57–60), almost 50% of EPS enzymatic secretion in the intestinal phase depends upon reflex activity of the duodenal-pancreatic nervous arc. As for the gastric phase of EPS, we have already noted that reflex activity starting from the antral region—that is, antral-pancreatic reflexes—plays a crucial role, and that atropine blocks approximately 60% of the hydrelatic and ecbolic components of EPS (53).

In the cephalic phase of EPS, cholinergic reflex activity also plays a fundamental role, synergistic with peptidergic participation (42–48).

Bicarbonate secretion of the pancreon units is subject to cholinergic influence. Acetylcholine potentiates secretin effects on centroacinar-ductal parenchyma. Vagotomy or atropine depresses the pancreon bicarbonate response to intraduodenal HCL infusion (58–64) without impairing secretin release. These data support the concept that secretin released from the duodenal-jejunal segment interacts at the pancreon level with intrapancreatic acetylcholine. The intraglandular levels of this neurotransmitter are determined by autonomic activity of the intrapancreatic ganglia, by reflex activity arriving from the central nervous system, that is, direct vagal innervation, and by activity of the intermediate autonomic nervous brains, "antral," "duodenal," and "celiac" (6–9).

Pancreon Modulation of Secretion

Pancreon modulation of secretion or braking can originate from the upper gastrointestinal tract via the vagus nerves or be elicited from the gut lower segments—ileum or colon. Braking mechanisms are essential to prevent supramaximal ecbolic stimulation which could trigger acute pancreatitis, for example cerulein pancreatitis. A suggestion of a brake mechanism in control of EPS is afforded by comparison of the maximal enzymatic secretory capacity obtained by a test meal with the level of secretion following an intravenous maximal dose of CCK (148–150). The capacity for fluid, bicarbonate, and enzyme induced intravenously is always greater than that elicited by endogenous stimulation. Thus, vagal excitation implies simultaneous involvement of positive (acetylcholine, bombesin) and negative (ENK, SOM, SP) components impinging on the pancreon. The lower values of the test meal when compared with the intravenous hormonal stimulation also implies participation of negative nervous reflex arc starting in the upper segments of the gastrointestinal tract and/or the release of peptides with an inhibitory effect on pancreon cells (PP, SOM, ENK, SP). Inhibiting mechanisms originating in the ileum and colon also brake pancreon activity and inhibit gastric and cholecystic motility and secretion. This negative feedback is both neural (adrenergic) and hormonal (pancreotone) (12, 36, 38, 100, 104, 105). Pancreatone is perhaps related to PYY, an N-terminal tyrosine, C-terminal tyrosine peptide, which belongs to the PP family. Blood levels of this peptide are raised after ingestion of protein and fats such as oleic acid. PYY is a powerful inhibitor of secretin-CCK induced EPS (151–153). Hyperglycemia is another pancreon brake. It has been proposed that hyperglycemia interferes with vagal efferent activity (154), but the mechanism is unknown.

Several peptides inhibit EPS when they are administered exogenously. Somatostatin, PP, and PYY are accepted as having physiologic involvement as well as pharmacologic activity. According to Schwartz (141), the instantaneous PP release after food ingestion or following vagal stimulation implies a "feed-forward inhibition" of EPS (Fig. 6, in part 1).

Analysis of PP release following stimulus of PP secretion under various physiologic states suggests a complex and intricate interplay, at pancreon level, between the endocrine and the three branches of the autonomic nervous system. Thus, CCK, bombesin, neurotensin, secretin, and VIP activate nerves that elicit release of PP from endocrine cells. Atropine blocks secretin and bombesin-evoked PP release. Bombesin, in humans, exerts excitatory and inhibitory influences on PP secretion. On the other hand, bombesin stimulates PP by vagal excitation and inhibits PP release by its hyperglycemic effect. In fact, blood glucose as well as fatty acid elevations suppress intrapancreatic cholinergic activity, via some as yet undetermined mechanism (73).

Analysis of PP blood concentration data affords clues concerning the anatomic pathways of pancreatic innervation. Thus, graded fundic or antral distension in humans evokes increased secretion of PP (154). Denervation of the fundus by proximal vagotomy almost abolishes this PP release. PP secretion, detectable in both portal and peripheral blood, is also enhanced by antral distension in healthy subjects as well as in duodenal ulcer patients (154). In addition, after antral distension in humans there is also a significant increase of glucagon concentration in the portal blood (154). This response is of the same magnitude in duodenal ulcer patients as in nonulcer subjects. On the other hand, the concentration of insulin in peripheral blood is completely unchanged by antral distension.

The foregoing clearly indicates the existence of gastropancreatic reflexes to the endocrine pancreas similar to those acting on the exocrine pancreas. It is interesting to speculate on the anatomic route by which nervous impulses inducing PP release arrive. The fact that in dogs, transection of the pylorus induces a 30% decline of PP blood levels (33) and that extragastric vagotomy does not have a significant influence (155) suggest that these nerve impulses to the PP endocrine cells, primarily located in the pancreatic head, pass through the antropylorus and perhaps through the duodenal wall before entering the pancreatic gland.

Analysis of Anatomic Pathways of Pancreatic Pain

Painful sensation arising in the pancreatic gland, as well as that originating in other abdominal viscera, is transmitted by afferent fibers which accompany sympathetic nerves and pass uninterruptedly through the sympathetic ganglia to reach the spinal cord via the posterior roots. Establishment of definite sites for referral of pancreatic pain would facilitate early recognition of pancreatic disease. Patterns of referred pancreatic pain have been studied by electric stimulation of the head, body, and tail of the pancreas following insertion of electrodes during elective surgery (156). Electrical stimulation of specific areas of the pancreas indicate that pain impulses transmitted through sympathetic pathways are referred to the respective dermatome levels at which the stimulus enters the spinal cord. Bliss et al (156) have come to four conclusions. First, pain from threshold stimulation of the head is distributed from the sixth thoracic dermatome to the eleventh and is predominantly located anteriorly just to the right of the midline. Right splanchnic blocks elevate the threshold for this pain. Second, pain from the body of the pancreas is distributed from the sixth thoracic dermatome to the eleventh and tends to be localized along the midline anteriorly. Both right and left splanchnic blocks affect the pain threshold. Third, pain from the tail of the pancreas localizes from the sixth thoracic dermatome to the first lumbar dermatome just to the left of the midline anteriorly. Left splanchnic blocks elevate the threshold of pain. And fourth, simultaneous stimulation of all three parts of the pancreas produces bandlike pain radiating to the back, typical of acute pancreatitis. The most ostensibly sensory structure of the pancreatic gland is Pacini's corpuscle. This shows signs of degeneration of its central nucleus after section of the splanchnic nerves (157–159).

Analysis of "Intermediate Autonomic Nervous Brains"

The intermediate autonomic nervous brains, "antral," "duodenal," and "celiac," are analogous to prevertebral ganglia and are primarily involved, anatomicophysiologically, with the pancreatic gland. Their principal role is integration and distribution of impulses arriving from diverse nervous impulses to different segments of the pancreatic gland. Moreover, they are nervous centers of reflex activity and appear to be involved in trophic reflexes to the pancreas (Figs. 2, 4, in part 1).

Recent studies of the peptidergic innervation of the rat and mouse stomach (160) disclose costoring of VIP and PHI in the same nerve fibers. These two peptides derive from the same precursor. All VIP/PHI fibers except the mucosal and perivascular also contain neuropeptide Y (NPY). Rat gastric mucosa has an abundant supply of GRP and VIP/PHI fibers and a sparse population of NPY and SP fibers. In the myenteric ganglia, the peptides detected are VIP/PHI/NPY, GRP, SP and ENK. The blood vessels receive a rich innervation of NPY fibers. In comparison, the density of fibers VIP/PHI, GRP, and SP is less. Vagal denervation does not affect the density or the distribution of the different peptidergic fibers. On the other hand, following sympathectomy, mucosal and perivascular fibers disappear. The rest of the peptidergic fibers are spared (160). It is evident that practically all the peptidergic nerves are intrinsic to the stomach wall, with the neuron cell body in the intramural plexuses. The NPY fibers are an exception; the subtype containing norepinephrine is extrinsic or sympathetic and the other, associated with VIP/PHI, is intrinsic to the stomach (160).

There are species differences in the anatomic pathways that traverse the celiac plexus. Thus, in cats all the cholinergic fibers pass through the celiac ganglion (37, 158). The pathways are unknown for dogs and rats. Histofluorescent studies indicate that the postganglionic adrenergic fibers of the stomach and pancreas in the rat pass through or originate in the celiac plexus (161). After celiac ganglionectomy there is no residual adrenergic pancreatic innervation. On the contrary, after truncal vagotomy there are no alterations in adrenergic fibers to the pancreas (161).

Much physiologic insight has resulted from analysis of the cholinergic, adrenergic, and peptidergic changes in the pancreas following the resection of the antral and/or duodenal autonomic nervous brains. Recently, distension of the proximal jejunum, with or without atropine, in canines (162) was reported to depress the rate of flow as well as the secretin-evoked bicarbonate and enzymatic EPS. Others have observed, also in dogs, that distension of a loop of jejunum induces depression of basal as well as of secretin-elicited EPS. These changes were prevented by previous atropinization or topical application of lidocaine to the jejunal mucosa (106). The effect of excitation of the celiac plexus in cats previously subjected to truncal vagotomy and bilateral splanchnicectomy was studied by Richins (13) in three groups of animals: a control group; a group receiving atropine pretreatment to block cholinergic fibers; and a group receiving ergotoxine pretreatment to block adrenergic fibers. Stimulation of the adrenergic component induced intrapancreatic vasoconstriction and opening of arteriovenous shunts with microcirculation bypass. The fall in the capillary flow was correlated with EPS depression reported under similar experimental conditions. Stimulation of the cholinergic component evoked vasodilatation, closing of the arteriovenous shunts, and enhancement of the capillary flow. Recently, Dreiling et al (164) have shown a significant enhancement of the intrapancreatic blood flow following celiac ganglion resection in dogs. Varga et al (165) reported that the celiac ganglion stimulation increased the death rate of bile-induced acute pancreatitis in canines fourfold. It is possible that reflex arcs integrated in the celiac ganglion play a pathogenetic role in human acute pancreatitis. Interruption of this arc reflex activity by means of novocaine celiac infiltration could explain the beneficial effects reported in this disease (166).

Vagosympathetic and Sympathovagal Pathways Inducing Secretory or Trophic Effects on Pancreas

Not much attention has been directed to vagosympathetic and sympathovagal reflexes in the physiologic control of pancreatic secretion. Yet in 1923 Ivy and McIlvain (167, 168) first observed that the presence of food in the stomach increased colonic motility via a vagovagal gastrocolic reflex. Subsequent observations suggested a vagosympathetic arc in dogs; electrical stimulation of the central end of the vagus nerves, either right or left, elicited gastric and intestinal relaxation which occurred even when the opposite nerve was sectioned. This motor response was accompanied by profuse secretion of thick mucus by the pyloric glands as well as an increase in blood pressure. The gastric response was abolished by simultaneous splanchnicectomy. In 1938, Tanturi and Ivy (169) reported that stimulation of the central end of one vagus, with the other intact, augmented bile secretion in the dog. Nevertheless, after bilateral vagotomy, electrical stimulation of either vagus nerve inhibited bile secretion via sympathetic impulses that reach the biliary tract passing through the spinal cord and splanchnic nerves.

Subsequently, Tansy et al (168) demonstrated that this inhibitory effect resulted from a reflex arc stimulating smooth muscle fibers in the extramural portion of the common bile duct rather than from the consequence of diminished secretion of bile by the liver. In other experimental work, Tansy and Kendall (168) showed that electrical stimulation of the central end of the vagus nerves in the cervical region increases the motor activity in the proximal colon in the dog. Gastric and duodenal distension have a similar effect. The induced colonic motor activity is not modified by transections at the level of the ileum, left colon, pelvic plexus, or lumbar segment of the spinal cord. On the other hand, colonic hypermotility is blocked by transection of the spinal cord at thoracic level.

These data suggest that the efferent limb of the reflex arc travels via the colonic nerves of the lumbar sympathetic chain. This reflex activity is abolished by atropine, implying that cholinergic fibers are present in the adrenergic nerves of the colon. Recent human studies revealed that a test meal enhances electric activity of the distal colon (170, 171). This arc reflex is also blocked by procaine topical anesthesia of the gastroduodenal mucosa, by anticholinergics, and by opioid blockers such as naloxone. The exact anatomic pathways, probably cord-mediated vagosympathetic, have not yet been defined. It is even possible that the reflex arc is integrated in the celiac plexus. Thus, it is evident that the cholinergic, adrenergic, and peptidergic systems are involved in the total integration of secretory and motor activity. Function-linking reflexes may be sympathetic-vagal. Sarles et al (172–174) reported experiments in dogs which showed that chronic irritation of the right splanchnic nerve with pumice powder triggers biliary hypertension. This response is abolished either by bilateral truncal vagotomy or cutting of the left vagus. Vagosympathetic reflexes elicit trophic changes in the pancreatic gland (34). Indeed, a series of experiments in the rat indicates the existence of a "great trophic circuit" formed by the pancreas, the vagal nerves (afferent limb), the central nervous system, the splanchnic nerves, and the celiac ganglia (efferent limb). Interruption of the afferent limb (truncal vagotomy) triggered the discharge of trophic impulses (adrenergic?) from the central nervous system, mainly directed to the pancreatic body-tail segment, which responded by hypertrophy and hyperplasia.

Interactions between Steroid Hormones and Neuroendocrine System at Pancreon Level

Our studies in dogs with hypophysectomy and adrenalectomy (175, 176) indicate involvement of ACTH and the adrenal steroids in secretin and/or CCK-induced EPS. Indeed, adrenal insufficiency causes a profound fall in volume of juice secreted, in bicarbonate concentration and output, and in amylase concentration and output. These changes were partially reversed by intravenous aldosterone and by infusion of isotonic sodium chloride. A striking finding following adrenalectomy was an ACTH-induced fall in volume and bicarbonate and amylase secretion. Similar findings in humans were reported by Gullo et al (177) with synthetic ACTH. Where and how this peptide exerts its inhibitory influence on the pancreon secretory response is unknown.

Recent studies in rats (178) and menopausal women taking estrogen (179, 180) indicate that bile-pancreatic secretion in the rat (178) and the secretin-evoked EPS in humans (179, 180) are responsive to interactions triggered by the activation of estrogen receptors in the cytosol of the pancreon cells. Indeed, in male rats subcutaneous administration of estradiol benzoate (50 μg) every other day for two weeks induced an increase of the hydrelatic and ecbolic parameters of basal bile-pancreatic secretion. Histologic examination of the exocrine and endocrine parenchyma disclosed structural changes. The acinar tissue showed marked depletion of zymogen granules. The Langerhans islets, following an initial period of hypertrophy, were reduced in size and cell mass. These findings may be the result of either direct mechanisms, that is, potentiation of interaction between neuroendocrine hormones and their receptors, or indirect mechanisms, that is, estradiol-evoked release of insulin, which augments the secretory effects of CCK and acetylcholine on pancreon units.

In menopausal women, estradiol-valerianate (4 mg/day) also alters the secretin-evoked pancreatic secretory response (179, 180). When given for short periods (one month), estradiol elicits an augmentation of EPS. On the other hand, when estradiol is administered for long periods (three to four months), it induces a significant decrease of secretin-induced EPS. The excitatory phase (short estrogen administration) results from activation of the cytosolic pancreon receptors. This enhances the normal potentiating interplay between estrogen and secretin receptors in acinar and ductular cell membranes. This mechanism may also explain the post-secretin hypersecretion observed in patients with alcohol hepatic cirrhosis, a condition in which hyperestrogenism has been demonstrated. The inhibitory phase (prolonged estrogen administration) is the consequence of a desensitization phenomenon (estrogen receptor down-regulation) and a lessening of the normal potentiating interaction between the receptors involved. Thus, the decline of plasma estradiol in menopausal women could play a role in the pathogenesis of diminished secretory capacity as well as the increasing incidence of chronic pancreatitis observed in aging women.

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Unusual Lesions of the Pancreas

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Abstract

The most common condition of the pancreas encountered on a general surgery service is pancreatitis, and the predominant tumor is ductal adenocarcinoma. Other neoplasms account for approximately 5% of pancreatic tumors. Unusual pancreatic lesions have an interesting and variegated clinical presentation due to their location and potential for hormonal activity. When possible, surgical excision remains the treatment of choice for most unusual lesions.

The most common abnormality of the pancreas encountered on a general-surgery service is pancreatitis, a benign inflammatory condition. Neoplasms of the pancreas can arise from the parenchyma of the exocrine pancreas or from the islets of Langerhans, the endocrine pancreas. Neoplasia of exocrine elements accounts for 95% of pancreatic tumors (1), chiefly arising from pancreatic duct cell epithelium. Less frequently, acinar or connective tissue elements of the pancreatic exocrine system may give rise to neoplasms. Neoplasia of the islets accounts for 5% of pancreatic tumors (1). In addition, there are some rare tumors of the pancreas whose cells of origin are uncertain. Anatomic anomalies and metastatic lesions involving the pancreas may also occur.

Since the majority of pancreatic lesions seen on a general-surgical service in a teaching hospital consist of pancreatitis and ductal adenocarcinomas, these other lesions are rarely encountered. In an attempt to draw attention to unusual lesions of the pancreas, we have retrospectively reviewed our experience at Cedars-Sinai Medical Center in 10 cases with unusual clinical or pathologic features.

Materials and Methods

The records of 9 patients who underwent treatment of rarely encountered lesions of the pancreas at Cedars-Sinai Medical Center were studied retrospectively. In addition, 1 patient had a unique finding at autopsy. All 9 surgical patients underwent exploratory laparotomy, and 8 had resectable lesions. Patients ranged in age from 7 weeks to 86 years (at the time of the surgery). Follow-up through December 1986 was obtained for 7 patients, with specific attention directed to the presence or absence of symptoms and evidence of pancreatic endocrine or exocrine insufficiency. (See Table).

Case Reports

Case 1. An 86-year-old white woman was in good health until 1 month prior to admission, when she noted increasing abdominal girth, gradual onset of back pain, and fatigability. At operation, an irregular, multilobulated retroperitoneal mass was found replacing approximately 90% of the pancreas, sparing only 3–4 cm of the head. The tumor measured 20 × 12 × 3 cm, extended from the diaphragm to 5 cm above the anterior superior iliac spine, and was densely adherent to the retroperitoneal structures (Fig. 1). The spleen was two and one-half times normal size. A near-

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TABLE

Unusual Lesions of the Pancreas, 10 Patients

Pt. no.	Age at operation	Diagnosis	Operation performed	Date	Postoperative follow-up
1	86 yrs	Myosarcoma	Subtotal pancreatectomy, splenectomy, liver biopsy	1980	Died after 1 year
2	62 yrs	Metastatic acinic cell carcinoma	Excisional biopsy of periaortic lymph node	1984	Died after 2 years
3	49 yrs	Cystadenoma of pancreatic head	Whipple procedure, cholecystojejunostomy	1954	Alive after 32 years with esophageal and gastric varices, encephalopathy
4	7 wks	Nesidioblastosis	Subtotal pancreatectomy, liver biopsy	1966	Retarded at 3 years
5	24 yrs	MEN-I with beta-cell adenomatosis; one focus of microcarcinoma	Subtotal pancreatectomy, omentectomy, splenectomy	1971	Lost to follow-up after 2 years
6	42 yrs	Centroacinar hyperplasia, alpha-cell hyperplasia	Subtotal pancreatectomy, splenectomy	1978	Died after 1 year
7	46 yrs	Carcinoid tumor	Subtotal pancreatectomy, splenectomy	1980	Alive after 6 years
8	29 yrs	Papillary cystic tumor	Distal pancreatectomy	1985	Alive after 1 year
9	60 yrs	Metastatic cystosarcoma phyllodes	Subtotal pancreatectomy, splenectomy, liver biopsy	1980	Died after 1 year
10	76 yrs	Intrapancreatic accessory spleen	Found at autopsy	1968	—

total pancreatectomy and splenectomy was performed. Microscopic examination revealed gigantocellular spindle cells and a fiber-forming sarcoma with areas of hyalinization and necrosis. There was evidence of sarcoma in the peripancreatic lymph nodes. The histologic diagnosis was myosarcoma.

Postoperatively, the patient regained her previously lost weight and remained asymptomatic for 7 months, when metastatic disease in the liver was found. She received radiation therapy but died 16 months after surgery.

Case 2. A 62-year-old white man presented with a 5-month history of left-upper-quadrant pain, which radiated to his back. At operation a stony hard mass was found occupying the distal pancreas. A periaortic lymph node was found to contain metastatic acinar cell carcinoma (Fig. 2). There was no evidence of liver pathology. No resection was performed in view of the demonstrated metastatic node.

The patient received neon particle therapy and experimental immunotherapy. One year after surgery, computerized tomography revealed metastatic disease in both lobes of the liver. The patient died 2 years after operation.

Case 3. A 49-year-old white woman underwent a pancreaticoduodenectomy, choledochoduodenostomy, cholecystojejunostomy, and gastrojejunostomy in 1954 for a 25 × 15 × 10 cm cystadenoma of the head of the pancreas (Fig. 3). Sixteen years later she developed obstructive jaundice and diabetes. A 15 × 7 × 5 cm polycystic mass was found extending into the porta hepatis and intimately adherent to the portal vein and hepatic artery. The common bile duct was dilated to 2.5 cm secondary to marked narrowing of the choledochojejunostomy and obstruction of the cystic duct.

This cystic mass was not resectable but was reduced in size by aspiration of 125 cc of thin, clear fluid. A new Roux-en-Y choledochojejunostomy was established 2 cm above the obstruction.

The patient continued to do well for another 16 years, when she was admitted with portal hypertension. Computerized tomography showed evidence of further intrahepatic extension of the neoplasm, suggesting malignant transformation of the original cystadenoma. The patient is alive 32 years following the initial operation.

Case 4. An infant girl, the second child of a 25-year-old black mother, was noted to exhibit macroglossia and slight hypotonia at birth. Nineteen hours after birth the infant began to have jerking movements of all extremities, mottling and duskiness of the skin, and apneic episodes. Symptoms improved after the administration of glucose. Blood sugar levels were found to be as low as 10 mg/dl through the first six weeks of life, although insulin levels were normal. There was no family history of carbohydrate disorders or neurologic disturbances.

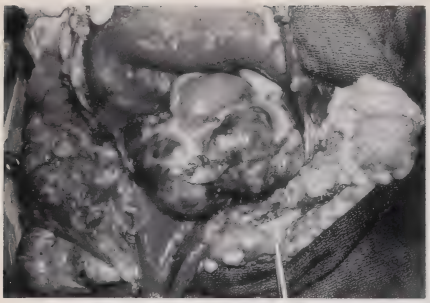


Fig. 1. Case 1. Myosarcoma of pancreas (operative photograph).

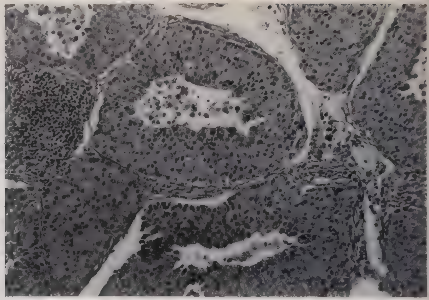


Fig. 2. Case 2. Acinic cell carcinoma (photomicrograph ×280).

On the forty-seventh day, 80% of her distal pancreas was resected and found to contain focal nodular hyperplasia of the beta cells of the islets of Langerhans (Fig. 4). Liver biopsy revealed glycogen depletion.

In follow-up at 3 years of age, the patient had obvious mental retardation and was unable to walk or talk. She was maintained on phenobarbitol for control of seizures. Blood sugars were normal.

Case 5. A 24-year-old Filipino woman with multiple endocrine neoplasia type I syndrome had symptoms of hypoglycemia for 18 months. She had galactorrhea and several episodes of amenorrhea. Ten months previously, she underwent resection of four of five parathyroid glands that showed adenomatous hyperplasia.

The patient underwent enucleation of a 3-cm islet cell adenoma from the head of the pancreas and a resection of the body and tail of the pancreas. Careful examination of the resected pancreas revealed at least 147 beta-cell adenomas (Fig. 5). Two years following surgery, the patient was doing well and did not require hypoglycemic agents.

Case 6. A 42-year-old black man presented with chronic relapsing idiopathic pancreatitis and diabetes. Eight months previously he underwent cholecystectomy, common bile duct exploration, and pancreatic ductal sphincteroplasty. His postoperative course was complicated by pylorospasm and gastric acid hypersecretion.

Because of unrelenting pain the patient underwent subtotal pancreatectomy. Special tissue stains and electron microscopy revealed alpha-cell hyperplasia and centroacinar hyperplasia. The patient died one year following operation owing to aspiration pneumonia and diabetic ketoacidosis.

Case 7. A 46-year-old white man noted epigastric pain, oily stools, intermittent diarrhea, and a 16-lb weight loss over 4 months. Retrograde pancreatogram revealed a sharp cutoff of the pancreatic duct at the midbody of the pancreas. Preoperative cytology was unrevealing.

A subtotal pancreatectomy and splenectomy

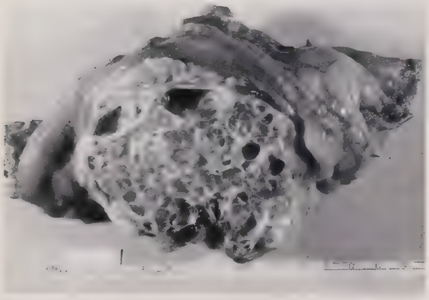


Fig. 3. Case 3. Cystadenoma of pancreas (gross photo).

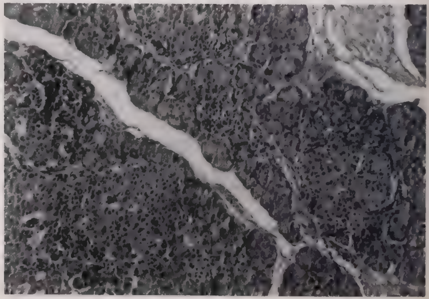


Fig. 4. Case 4. Nesidioblastosis of infant pancreas (photomicrograph ×280).

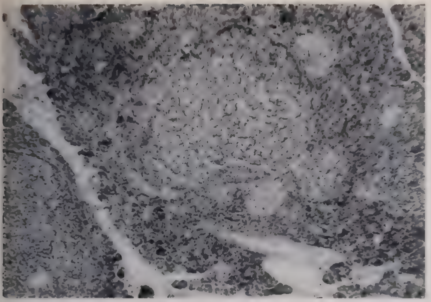


Fig. 5. Case 5. Multiple adenomas of pancreas (photomicrograph ×280).

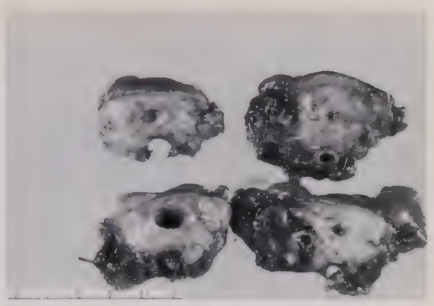


Fig. 6. Case 7. Carcinoid tumor obstructing pancreatic duct (gross photograph).

were performed. Microscopic evaluation revealed a 5-mm carcinoid tumor obstructing the pancreatic duct (Fig. 6). Computerized tomography of the abdomen 6 years after operation was normal, and the patient is currently doing well.

Case 8. A 29-year-old black woman had a history of abdominal trauma 4 weeks prior to examination and complained of upper-abdominal pain. Computerized tomography revealed an 8-cm cystic lesion of the pancreatic tail, which persisted after 6 weeks of observation.

The patient underwent distal pancreatectomy without splenectomy, and a papillary cystic tumor was found measuring 7 × 7 × 5 cm (Fig. 7). She has done well in the 15 months since surgery.

Case 9. A 60-year-old white woman had a large epigastric mass. Three years prior to admission she had undergone a right simple mastectomy for a 2,500-gm cystosarcoma phyllodes. At laparotomy a 16 × 16 × 9 cm tumor mass replaced the body and tail of her pancreas (Fig. 8). It had a well-defined pseudocapsule, but the pancreatic duct was infiltrated and deformed by the tumor. The histology of the pancreatic tumor was identical to that of the breast tumor (Fig. 9). The patient died within a year of surgery.

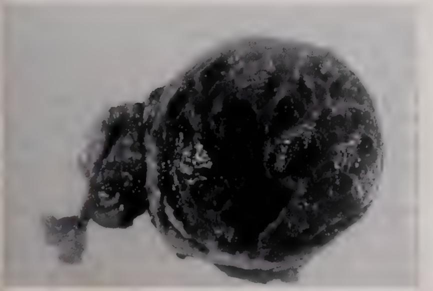


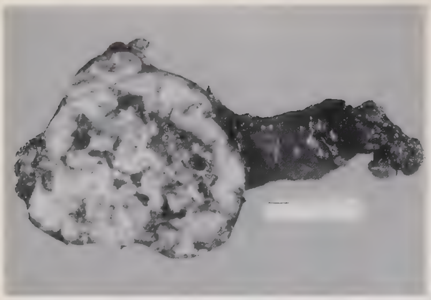
Fig. 7. Case 8. Papillary cystic tumor of pancreas (gross photograph).

Case 10. A 76-year-old white man was found at autopsy to have an intrapancreatic accessory spleen, located within the body of the gland (Fig. 10). No other pancreatic anomalies were noted.

Discussion

The predominant pancreatic tumor seen on a surgical service is adenocarcinoma, which accounts for approximately 25,000 deaths yearly in the United States (2). Other neoplasms of the pancreas are observed much less frequently. Pancreatic neoplasms are classified most simply by the cell of origin (endocrine versus exocrine) and by malignant potential (3). Malignant lesions of the exocrine pancreas (duct cells, connective tissue, and acini) include ductal adenocarcinoma and, less frequently, tumors such as myosarcoma and acinar cell carcinoma. Benign pancreatic exocrine neoplasms, including cystadenoma, are rare.

Neoplasms of the endocrine pancreas can display benign or malignant characteristics and elaborate the hormones produced by their cell of origin; insulinomas derived from the beta cells, glucagonomas derived from alpha cells, gastrinomas from delta cells, and carcinoids from enterochromaffin cells are examples. These tumors have been described as types of apudomas, all of which are felt to derive from cells of neural crest origin. Rare benign pancreatic neoplasms, such as papillary cystic tumor, arise from cells of uncertain origin. Metastatic disease to the pancreas is not uncommon. Breast, lung, and melanoma from the skin are common tumors that are metastatic to the pancreas (4).



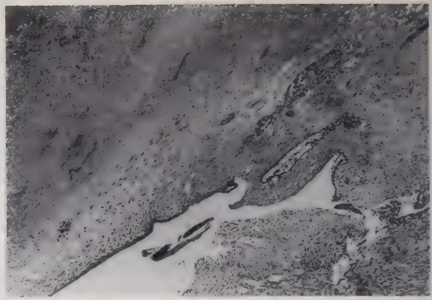


Fig. 8. **Case 9.** Cystosarcoma phyllodes metastatic to pancreas (gross photograph). **Fig. 9.** Same patient. Cystosarcoma phyllodes of pancreas (photomicrograph ×280).

These unusual tumors vary in their presentation, signs, symptoms, and prognosis. A brief description of the lesions we have discussed follows.

Myosarcoma. Primary connective tissue tumors of the pancreas are very rare. Some reports in the older literature may actually represent retroperitoneal sarcomas with extension into the pancreas. As illustrated by Case 1, myosarcomas of the gastrointestinal tract can be highly invasive and are thus associated with a very high mortality rate. Survival of up to 11 years has been reported after surgical resection (3).

Acinic Cell Carcinoma. These tumors account for less than 1% of pancreatic malignancies (4) and affect patients in a wide age distribution. A syndrome of panniculitis, eosinophilia, and polyarthritis has been described in some patients (5). Prognosis and treatment are similar to those of ductal carcinomas (4).

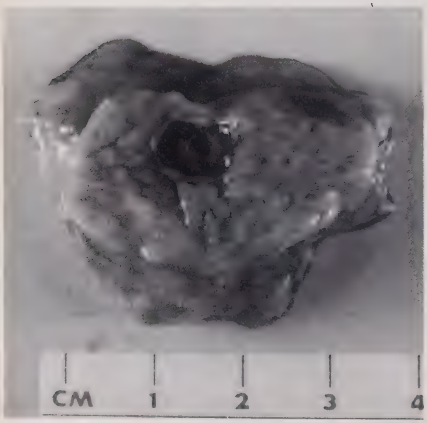


Fig. 10. **Case 10.** Intrapancreatic accessory spleen (gross photograph).

Cystadenoma. Cystadenomas represent 4%–10% of all cystic lesions of the pancreas (6), with over 300 cases reported in the world literature. These tumors may occur in any portion of the pancreas and are usually large, rounded, lobulated, well-encapsulated masses, which may compress adjacent structures (7). The cyst walls are lined by regular cuboidal cells in a single layer (3). As in Case 3, most tumors are slow growing. Two kinds of cystic neoplasms have been described: aggressive mucinous cystadenoma and benign, glycogen-rich cystadenoma (7). The preferred treatment of both is total excision. It is critical that these lesions not be confused with pseudocysts of the pancreas, which could lead to inappropriate treatment by internal or external drainage.

Nesidioblastosis. Nesidioblastosis was initially described as a diffuse proliferation of islet cells. More recently, islet cell hyperplasia and hypertrophy, microadenoma, and adenomatosis have been added to the original definition (8). The clinical presentation is dominated by the symptoms of hypoglycemia. In infants it is the most common cause of hypoglycemia. If not identified and treated early, the disease will result in irreversible brain damage, as in Case 4. Medical management usually fails to stabilize glucose levels in a safe range, and prompt surgical intervention is recommended (9). There is debate over the proper operative procedure, ranging from enucleation to 90% pancreatectomy (8, 10).

Alpha-Cell Tumors. By 1980, 47 cases of alpha-cell tumors had been identified (11). A classical clinical syndrome of diabetes, necrolytic migratory erythema, stomatitis, anemia, and weight loss marks the disease. The primary treatment is surgical excision. Chemotherapy with streptozotocin has shown fair results in selected patients (12).

Carcinoid. Over 4,000 carcinoids in various anatomic locations have been described, but pancreatic carcinoid is uncommon (0%–6%) (13, 14). Symptoms may be secondary to the location of the tumor or rarely (7%) (15) to the action of serotonin and other hormones producing the carcinoid syndrome. Surgical excision is the treatment of choice.

Papillary Cystic Tumor. This type of pancreatic tumor is rare, with 31 cases reported by 1986 (16). It exclusively affects young women. The histiogenesis remains uncertain, but electron microscopy and immunocytochemical studies are consistent with a tumor of ductal or centroductular origin (4). The prognosis following surgical resection is good.

Cystosarcoma Phyllodes. This uncommon neoplasm of the breast is similar to the fibroadenoma in structure but histologically demonstrates increased stromal cellularity and sometimes has a malignant behavior (17). When malignant, its primary site for metastasis is the lung. There are no reported cases prior to this one of cystosarcoma phyllodes metastatic to the pancreas.

Intrapancreatic Accessory Spleen. The reported incidence of accessory spleen is 10%–31% (18, 19), and in most cases they are located at or near the hilus of the spleen. Intrapancreatic accessory spleens are very rare.

The cases described well illustrate the interesting and variegated clinical presentation of unusual pancreatic lesions. Some may reach a large size with silent growth, but others come to the attention of physicians early because of ductal obstruction or endocrine abnormalities. In almost all cases the treatment of choice is surgical excision.

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Early Combination of Dopamine Agonist and Levodopa in the Treatment of Parkinson's Disease

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The discovery of striatal dopamine deficiency and its substitution treatment with levodopa has meant a great step forward in the management of Parkinson's disease and represents one of the major therapeutic advances in clinical neurology. However, it has not resolved the long-term management of Parkinson's disease because levodopa—a symptomatic replacement agent—does not prevent the natural progressive course of the disease and does not have a permanent beneficial effect. Furthermore, many other late problems of long-term levodopa therapy arise, especially the different kinds of fluctuations in disability (1–5). Indeed, fluctuations in disability become increasingly frequent during the course of treatment, involving about 50% of patients after five years of treatment and nearly all patients after 10–12 years (5). For these reasons the management of Parkinson's disease has in recent years become more difficult and new strategies are needed. During the past few years I have been studying whether dopamine agonist therapy alone or in early combination with levodopa might offer a better long-term treatment than high-dose levodopa alone (5–7).

Dopamine Agonist Alone

Bromocriptine. Long-term treatment of de novo parkinsonian patients clearly showed that only a small proportion of patients seem to have really long-term benefit and tolerance during treatment with bromocriptine alone (6, 7). Thus after three years 28%, and after five years only five patients (7%), were still undergoing this treatment. The main reasons for withdrawal of bromocriptine therapy during the five years of treatment were insufficient therapeutic response (53%) and distressing side effects in 24 patients (32%); eight patients (11%) died during the five years of treatment and one patient had loss of control (7).

During long-term treatment with an optimal dose of bromocriptine the mean improvement in parkinsonian disability was only moderate, and clearly decreased over the period of treatment (Table 1). Therefore, levodopa had to be added to the regimen of many patients, thus forming the early combination of bromocriptine and levodopa. The therapeutic responses were very good with regard to the development of fluctuations in disability. During treatment with bromocriptine alone for five years, no end-of-dose disturbances developed; only two patients had randomly occurring freezing episodes, and a few had peak-dose dyskinesias (Table 1).

Other Dopamine Agonists. Treatment with other dopamine agonists seems to result in roughly similar long-term therapeutic responses to those with bromocriptine. Thus after three years of treatment, 5 of 20 patients treated with pergolide (25%) and 6 of 30 patients treated with lisuride (20%) had enough therapeutic benefit and tolerance. The main reason for withdrawal of treatment was insufficient therapeutic response (60% and 67%, respectively). During long-term treatment with an optimal dose of pergolide or lisuride, the mean improvement in parkinsonian disability was only mild or moderate. More sig-

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This paper was an invited contribution to the January 1988 issue, "Parkinson's Disease, Alzheimer's Disease, and the Aging Brain," to honor Prof. M. D. Yahr, Chairman of the Dept. of Neurology, Mount Sinai School of Medicine (CUNY), New York, but was received too late to be published in that issue.

TABLE 1

Dosage, Improvement in Parkinsonian Disability (PD), and Fluctuations in Disability during Long-Term Treatment of Parkinsonian Patients with Bromocriptine
(Mean ± SEM)

	Duration of treatment (years)				
Variable	1 (N = 32)	2 (N = 22)	3 (N = 21)	4 (N = 13)	5 (N = 5)
Dosage (mg)	37.9 ± 5.0	31.5 ± 5.3	28.0 ± 4.3	26.2 ± 4.2	26.0 ± 9.4
Improvement of PD (%)	28 ± 2	25 ± 3	15 ± 3	3 ± 7	18 ± 8
Fluctuations in disability					
End-of-dose	0	0	0	0	0
Random freezing	0	0	1	1	0
Peak-dose dyskinesia	7	5	2	2	1

nificantly, however, neither end-of-dose disturbances nor dyskinesias developed during three years of treatment with pergolide or lisuride (8).

Early Combination of Dopamine Agonist and Levodopa

Bromocriptine. The early combination of bromocriptine and levodopa was instituted in 42 parkinsonian patients who showed insufficient therapeutic response to initial bromocriptine treatment. These patients were compared originally with 217 parkinsonian patients who had been treated with levodopa and a decarboxylase inhibitor, of whom 196 patients were followed up for five years. There were no statistically significant differences between these two parkinsonian patient populations, although they were not randomized groups (6, 7).

Side effects led to the withdrawal of the treatment in 12 patients; 3 patients died and 2 patients had loss of control during the five-year period. Thus the long-term tolerance of combined treatment seems to be significantly better than for bromocriptine alone.

During five years' combined treatment, the mean daily doses of bromocriptine were relatively low and those of levodopa significantly ($P < 0.001$) lower than in patients treated with levodopa alone (Table 2). During five years of treatment, however, there was a clear-cut decrease in the degree of therapeutic response of the patients in both treatment groups (Table 2).

During combined treatment with bromocriptine and levodopa over a period of five years, there developed significantly fewer end-of-dose disturbances (end-of-dose akinesia, early-morning akinesia, and off-period freezing episodes) than during treatment with high-dose levodopa alone (Table 3). Furthermore, five years' combined treatment resulted in significantly ($P < 0.001$) fewer peak-dose dyskinesias than did levodopa-only treatment (Table 3). On the other hand, random freezing episodes occurred in both treatment groups without any significant statistical difference.

TABLE 2

Dosage and Improvement in Parkinsonian Disability (PD) during Long-Term Treatment of Parkinsonian Patients with Levodopa Alone and in Early Combination with Bromocriptine
(Mean ± SEM)

	Duration of treatment					
	3 years		4 years		5 years	
Variable	Levodopa (N = 217)	Levodopa + bromocriptine (N = 28)	Levodopa (N = 204)	Levodopa + bromocriptine (N = 26)	Levodopa (N = 196)	Levodopa + bromocriptine (N = 25)
Dosage (mg)						
Levodopa	798 ± 12	660 ± 35***	793 ± 13	631 ± 40***	795 ± 14	592 ± 36***
Bromocriptine		16.6 ± 1.9		13.8 ± 1.5		13.7 ± 1.7
Improvement of PD (%)	37 ± 1	39 ± 3	31 ± 2	32 ± 4	23 ± 1	23 ± 5

*** $P < 0.001$ as compared to levodopa alone

During long-term treatment, in five patients the therapeutic response to bromocriptine alone deteriorated so significantly that it was necessary to add levodopa to their regimen at a comparatively late stage, after 45–53 months of treatment. This late combination resulted in a significant further improvement in parkinsonian disability (7). During the further treatment of these patients up to five years, no fluctuations in disability developed, but peak-dose dyskinesias occurred in two patients (Table 3).

Other Dopamine Agonists. Early combination of levodopa and pergolide or lisuride (8) resulted in long-term responses similar to response to bromocriptine therapy. These findings give further support to the primary findings on response to bromocriptine and to the value of the early combination of dopamine agonist and levodopa as a new strategy in the treatment of patients with Parkinson's disease.

TABLE 3

Occurrence of Fluctuations in Disability during Long-Term Treatment of Parkinsonian Patients with Levodopa Alone and in Early Combination with Bromocriptine for Five Years

	Levodopa (N = 196)		Levodopa + bromocriptine (N = 25)		(N = 30)[x]	
Disability	N	(%)	N	(%)	N	(%)
End-of-dose akinesia	67	(34)	1**	(4)	1***	(3)
Early-morning akinesia	46	(24)	1*	(4)	1*	(3)
Nocturnal akinesia	37	(19)	1	(4)	1*	(3)
Freezing episodes, dose-related	38	(19)	0*	(0)	0**	(0)
Freezing episodes, random	33	(17)	2	(8)	2	(7)
Early-morning dystonia	24	(12)	1	(4)	1	(3)
Daily dystonia	36	(18)	2	(8)	2	(7)
Peak-dose dyskinesia	124	(63)	6***	(24)	8***	(27)

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ as compared to levodopa, Mantel-Haenszel test.

[x] Including 5 patients with late combination after 45–53 months of treatment with bromocriptine alone.

Possible Mechanisms of Action of Early Combination

Combined treatment with dopamine agonist and levodopa seems to give therapeutic responses with a lower levodopa dosage than with the drug used alone. This lower dosage may in itself be an important factor in decreasing the risk of long-term complications (9). But the prevention of fluctuations in disability, especially end-of-dose failure, may result also from other factors. Indeed, the longer pharmacokinetic action of dopamine agonist on striatal dopamine receptor level than with levodopa alone may affect the therapeutic responses obtained.

On the other hand, it has been suggested that fluctuations, especially end-of-dose disturbances, might be due to a failure in the synthesis, storage, and release of dopamine in the nigrostriatal dopamine neurons because of faulty feedback control via presynaptic D-2 dopamine autoreceptors (10). According to this hypothesis, in the early phase of levodopa therapy, a given, unphysiologically high dose of levodopa may result in a normal, controlled release of dopamine and a smooth therapeutic response. This is claimed to be due to the capacity of nigrostriatal neurons to store the extra dopamine metabolized, because the feedback control is still functioning normally in the remaining nerve terminals. However, in the later phase of levodopa therapy, because of failure in the feedback control, the decreased storage capacity of dopamine in the striatal nerve endings may lead to an uncontrolled and excessive but short-lasting release of dopamine after each single dose of levodopa. In support of this hypothesis, recent PET studies have demonstrated decreased storage capacity of striatal dopamine in end-of-dose failure (11).

It is possible that early combined treatment with levodopa and a dopamine agonist, having a great affinity for presynaptic D-2 autoreceptors, might maintain the normal functioning of striatal dopamine neurotransmission for a longer period than does levodopa alone. Indeed, according to experimental studies, bromocriptine is able to block levodopa-induced changes in the striatal dopamine receptors (12).

It has been suggested that conformational changes in dopamine receptors induced by dopamine could explain the synergistic effect of levodopa and dopamine agonist (13). On the other hand, according to experimental studies, dopamine-induced stimulation of D-1 receptors potentiates the action of dopamine agonist on D-2 receptors (14). Thus, an early-therapy combination of dopamine agonist and levodopa seems to sustain a better balance between postsynaptic D-2 and D-1 receptors and presynaptic D-2 autoreceptors than high-dose levodopa alone. It is thus possible to maintain the normal functioning of striatal dopamine neurotransmission for a longer period than does levodopa alone, resulting in better management of Parkinson's disease with fewer fluctuations in disability.

Summary

It appears advisable that the management of parkinsonian patients should begin in the early phase of the disease with a combination of a low, submaximal dose of a dopamine agonist and levodopa.

It is possible to begin treatment using both drugs together or using either drug alone. In practice, I suggest that treatment be initiated with dopamine agonist alone, and that levodopa should be added if the therapeutic response is insufficient.

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Breast Size, Endogenous Estrogens, and Breast Cancer: A Review with Hypothesis

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The role of endogenous estrogens in breast cancer has long been a subject of interest. The breast is much less responsive to the tumor-promoting effects of estrogens than is the endometrium; estrogens, nonetheless, appear to be necessary for breast carcinogenesis (1). We suggest that the role of endogenous estrogens is solely to increase breast size and the amount of glandular tissue susceptible to malignant transformation. In physiologic concentrations, estrogens appear to have no other carcinogenic effect. In this report, epidemiologic and experimental evidence is presented to support this hypothesis.

Racial, Geographic, and Other Variables

There is marked variation in the rate of breast cancer in different areas of the world. In women at age 50, the incidence of breast cancer is about six times higher in the United States than in Japan or Taiwan (2). Interest in dietary fat as a possible explanation of this disparity has been stimulated by the strong correlation between national per capita consumption of fat and age-adjusted rates of breast cancer (3). However, other studies of breast cancer rates in population groups provide an inconsistent picture. For example, rates of breast cancer among orders of nuns who consume little or no meat were similar to those in the general British population of single women (4).

Furthermore, the breast cancer incidence in Japanese-American women still falls considerably below that for white women; and the rates of breast cancer for Japanese migrants and their daughters move more slowly toward the level of the adopted country than do rates for many other forms of cancer (5).

The factor that may be responsible for the lower breast cancer incidence is breast size. Oriental women, even those living in the United States, have considerably smaller breasts than Caucasians. One brassiere manufacturer reports selling A-cup brassieres almost exclusively to orientals living on the West Coast. In contrast, the same manufacturer sells predominantly B-cup and C-cup brassieres to the Caucasian women living in the Southwest and Middle West (6).

The probability of any single cell in a population becoming malignant in a given period of time may be compared to the chance of turning up heads on the toss of a coin. If a single coin is tossed, the probability is 50%. However, if a hundred coins are tossed, the chance of one turning up heads is considerably greater than 50%. By analogy, the larger the breast, the more glandular cells and, therefore, the higher the probability that a single cell, or multiple cells, will become malignant in a given period.

This line of reasoning, of course, may also explain why men have only 1% as much breast cancer as women (1). Because they have many fewer glandular cells vulnerable to malignant transformation, one would expect their breast cancer rate to be considerably lower.

More evidence supporting the relationship between breast size and breast cancer is provided by the size difference between the left and right breasts. In most women, the left breast is larger than the right (7), and there is a 6% to 13% excess of left-sided breast cancers among premenopausal and postmenopausal patients (8). Other studies have shown that the left breast develops cancer in 52% of cases, the right breast in 47%, and in 1% the disease is bilateral (7).

But there is still considerable controversy

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TABLE

Estrogen Receptor Status and Age at Onset in a Group of Women with Breast Cancer

	Smokers	Nonsmokers	Significance
Estrogen receptor			
positive	13	11	$chi^2 = 0.02$
negative	12	11	$p > 0.9$
Age at cancer onset (yrs)	51.8 ± 11.6	54.4 ± 15.3	$t = 0.65$
No. of women	25	22	$p > 0.5$

over breast size and breast cancer (7). For example, mammary fat, as well as glandular tissue, plays a substantial role in breast size (9). Yet it is logical to assume that the amount of glandular tissue is important for carcinogenesis.

Role of Estrogen

The breast size hypothesis may explain the lack of a relationship between endogenous estrogen fluctuation and breast cancer incidence. Neither high nor low endogenous estrogens have any effect in breast carcinogenesis.

Cigarette smoking is associated with an important antiestrogenic effect. Female smokers have decreased luteal phase urinary excretion of estrone, estradiol, and estriol (10). Moreover, there is a decreased incidence of endometrial cancer in smokers (11), but no protective effect against breast cancer (12). Our own data support the latter finding. We have noted that the incidence of the tumor estrogen receptor and the age at onset of the cancer are not significantly different statistically in smokers and nonsmokers (Table).

However, urinary estrogens are no higher in women with breast cancer than in the general population. Even the hormone excretion of high-risk groups does not differ from that of normal-risk groups (2). And estrogen-secreting tumors, which promote endometrial cancer, have no effect on breast cancer (1).

Early menarche and late menopause increase the risk of breast cancer (1). Although lengthened estrogen exposure has been suggested to be the cause of this increase, it might instead be related to another hormone, prolactin, also implicated in human and rat breast cancer (13).

Like estrogen, prolactin rises sharply at menarche and falls again at menopause (14, 15). This fluctuation can explain why premenopausal castration protects against breast cancer, whereas smoking does not. The explanation is that smoking causes only decreased estrogens, whereas castration induces premature menopause, which also lowers prolactin levels.

Thus, the only role of endogenous estrogens in breast cancer may be their promotion of breast enlargement and increased amounts of glandular tissue. In physiologic quantities, endogenous estrogens probably have no other effect.

Summary

Endogenous estrogens probably promote breast cancer only by increasing the amount of glandular tissue within the breast. For this reason, diminished estrogen production in smokers does not protect against breast cancer, though it does protect against uterine cancer. Castration before menopause diminishes breast cancer risk because it reduces prolactin levels as well as estrogen levels.

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Elimination of Graft Hemorrhage In Heparinized Patients with a Collagen-Coated Dacron Prosthesis

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Abstract

This is a pilot study of a new collagen-coated Dacron prosthesis. In a series of 17 patients undergoing operation for replacement of the ascending aorta, aortic patch angioplasty, and construction of internal jugular-right atrial and right ventricular-pulmonary artery conduits, hemorrhage through the interstices of the graft has been virtually eliminated even in patients requiring heparinization and cardiopulmonary bypass. Because the collagen is covalently bonded to commercially available knitted prostheses, the grafts retain extraordinary ease of handling. These factors, in addition to the absence of clinical evidence of embolization over an average follow-up period of 18.7 months (range 6–36 months) have encouraged us to continue our use of this graft as the prosthesis of choice in patients requiring vascular reconstruction.

The use of conventional Dacron grafts in patients requiring systemic heparinization is frequently complicated by excessive hemorrhage through the interstices of the graft despite pretreatment with clotted blood or with platelet-rich plasma followed by autoclaving (1). To obviate this problem, conventional knitted grafts have been treated with purified collagen fibers that have been reconstituted and covalently bonded to the Dacron (Tascon Medical Technology, A Division of Medtronic Blood Systems, Inc., 7000 Central Avenue, NE, PO Box 1350, Minneapolis, MN 55440). This report presents our experience with 17 such grafts, all but 4 of the 17 patients requiring systemic heparinization for cardiopulmonary bypass.

Materials

Commercially available Dacron grafts were coated with collagen purified from bovine skin and salt-precipitated. The collagen fibers were reconstituted and covalently bonded to the Dacron. Additional biocompatible protein materials were added to control final porosity to an average of 0.24 cc H_2O/cm^2 (range 0.0 cc/cm^2 to 1.2 cc/cm^2). The graft-biologic material complex was then cross-linked with 0.35% glutaraldehyde in buffered electrolyte solution (Tascon Medical Technology).

Methods

Seventeen patients have received collagen-coated Dacron grafts. Thirteen required cardiopulmonary bypass, of which 9 were performed with bubble oxygenators and 4 with membrane oxygenators. The average pump time was 219 min (range 121 to 358 min). Nine grafts were used to replace the ascending aorta (Table). Of these, there were 7 acute dissections of the ascending aorta, all but one requiring simultaneous aortic valve replacement and either reimplantation or saphenous vein bypass of the coronary arteries. There were 2 patients with ascending aortic aneurysm not requiring dissection, but requiring aortic valve replacement and coronary

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TABLE
Procedures Performed Using Collagen-Coated Dacron Prosthesis (17 Patients)

Procedure	No. of pts.
Aortic grafts	9
Aortic dissection	7
Aortic aneurysm	2
Aortic patch angioplasty	6
Coarctation	3
Repair friable aorta	1
Repair calcified aorta	1
Correction supravalvular aortic stenosis	1
Right internal jugular-right atrial conduit	1
Right ventricular-pulmonary artery valved conduit	1

reimplantation. One patient received a porcine-valved conduit from the right ventricle to the pulmonary artery. Aortic patch angioplasty was required for repair of a friable aorta (1 case), correction of supravalvular aortic stenosis (1 case), and for enlargement of a calcified ascending aorta to allow closure without tension following aortic valve replacement (1 case).

Four procedures did not require cardiopulmonary bypass. These included, in three patients, aortic patch angioplasty for coarctation of the descending thoracic aorta, and in one patient, right internal jugular vein to right atrium conduit during repair of a ruptured subclavian artery aneurysm.

Results

There have been 4 deaths in this series. The first death occurred in an obese 63-year-old woman with a ruptured subclavian aneurysm. Brisk hemorrhage was encountered during sternotomy. Division of the left innominate vein was performed to facilitate exposure. Interestingly, this patient had absence of the right innominate vein. Cerebral venous drainage had been retrograde in the right internal jugular vein through intracerebral collaterals to the left internal jugular vein, thence to the left innominate vein which drained via an enormous left internal mammary vein into the azygous system. There was no right or left superior vena cava; thus, division of the left innominate vein interrupted all cerebral venous drainage. For this reason, a 22-mm collagen-coated graft was anastomosed end to side to the junction of the right internal jugular and subclavian veins and to the right atrial appendage. There appeared to be excellent flow through the graft. The subclavian artery aneurysm had previously been resected and replaced with a 6-mm Gortex graft. The patient died in the postoperative period from neurologic complications.

The second death occurred in a 50-year-old man with an acute type II aortic dissection with a prior history of multiple myocardial infarctions. The ascending aorta and aortic valve were replaced with a valved conduit consisting of a 28-mm collagen-coated graft and a 25-mm St. Jude valve. Because the right and left coronary ostia were severely arteriosclerotic and rigid, saphenous vein bypass grafting was performed to the left anterior descending, diagonal, first and second circumflexes, right ventricular marginal, and right posterior descending coronary arteries. Though initially able to maintain normal hemodynamics, the patient gradually developed right ventricular failure and died despite the use of inotropic agents and intraaortic balloon counterpulsation.

The third death occurred in a 59-year-old man with an acute aortic dissection, who had undergone two prior aortic valve replacements. The aorta, which was firmly adherent to the sternum, was entered during the sternotomy. Low flows were required for control of bleeding prior to establishing deep hypothermia. The ascending aorta was replaced with a 33 mm collagen-coated graft. The patient died of multisystem organ failure on the third postoperative day.

The fourth death occurred 5 months postoperatively in a patient who had undergone an uneventful patch angioplasty of a coarctation of the aorta at the age of 6 months. The patient had known aortic stenosis that was to have been treated at a second-stage procedure.

Other than the fourth case, all deaths could be explained by intraoperative events. In the fourth case, death was probably the result of aortic stenosis. There have been no late deaths.

Except for a minor degree of weeping seen through the interstices of the graft material for a few minutes after declamping, there was no bleeding noted through the grafts, despite continued exposure to heparinized blood. This has not been our experience with preclotted grafts, which, with continued exposure to heparinized blood, develop substantial interstitial hemorrhage.

Our patients have now (at the time of writing) been followed up for an average of 18.7 months (range 6–36 months) with no clinical evidence of distal embolization. The one patient with a valved conduit has undergone 2-D echocardiography, and after 36 months has a normally functioning porcine valve with no evidence of intraluminal peel formation. Because no late deaths have occurred, no long-term evaluation of implanted graft material has been possible.

Discussion

Our experience with the collagen-coated graft has confirmed the experimental prediction that covalent bonding of collagen to a knitted Dacron substrate dramatically reduces graft porosity and renders it virtually impervious to heparinized blood, despite prolonged exposure during cardiopulmonary bypass. Some weeping of blood through grafts placed in the systemic circulation has been observed transiently upon initial release of aortic cross-clamping, but the weeping has been minor and has generally stopped prior to the administration of protamine. The weeping phenomenon has not been observed in the 2 grafts placed in the venous circulation.

Collagen coating applied to a knitted Dacron substrate has resulted in a low-porosity graft which retains the extraordinary ease of handling of knitted prostheses. We have not observed suture line bleeding associated with needle holes through the collagen using 3-0, 4-0, or 5-0 cardiovascular sutures. Although the manufacturer discourages handling of the collagen lining with a forceps, we have applied small side-gripping vascular clamps to these grafts in order to perform aortocoronary anastomoses and have not observed bleeding through the graft at the clamping site. Whether fragments of collagen flaked off the graft consequent to clamping cannot be answered at this time, and it is recommended that aortocoronary anastomoses be performed with the aorta cross-clamped.

Laboratory studies of this prosthesis in animals have attempted to define the surface characteristics of the collagen surface after long-term exposure to blood (Tascon Medical Technology). Experiments involving the observation of iodine 125 fibrinogen sorption and chromium 51 platelet adherence to the collagen surface revealed minimal deposition after three months, and extensive covering of the prosthesis with endothelial cells was observed after 6 months of implantation in the right ventricular outflow tract in dogs (2). Because all but one of the deaths in this series were intraoperative, the fate of the collagen surface after prolonged exposure in the human circulation cannot be addressed at this time. Our longest follow-up has been 3 years in the patient with the porcine valved conduit, during which time repeated 2-D echo examinations have failed to reveal the intraluminal peel described in the Mayo Clinic experience (2).

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Systemic Lupus Erythematosus of the Central Nervous System: 1. Classification, Epidemiology, Pathology, Diagnosis, and Therapy

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Abstract

The central nervous system (CNS) manifestations of the chronic autoimmune disease systemic lupus erythematosus (SLE) are reviewed. SLE-CNS dysfunction is broadly divided into neurologic and psychiatric clinical categories. The distinct clinical entities within these broad categories are fully described. Diagnostic criteria employed to verify the presence of SLE-CNS dysfunction, including laboratory serum and cerebral spinal fluid analyses as well as radiologic and other multimodality diagnostic tools, are compared and contrasted with respect to sensitivity and specificity. Choices and combinations of therapeutic modalities, including corticosteroids, immunosuppressive and neuroactive pharmacotherapy, and plasmaphoresis, are discussed and reviewed. In addition, the epidemiology and pathology of the disease are outlined. Detailed analysis of the pathologic, laboratory, and radiologic characteristics of patients with SLE-CNS lays the groundwork for the presentation, in Part 2, of a unifying molecular theory that may account for the diversity and multiplicity of the disease.

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease characterized by remissions and exacerbations, and by its effects on multiple organ systems, including skin, joints, cardiopulmonary, gastrointestinal, renal, hepatic, hematologic, and peripheral and central nervous systems (1). The term "lupus" is a Latin derivative meaning wolf, and refers to the characteristic butterfly erythematous rash often described in SLE patients. Central nervous system (CNS) manifestations of SLE were first described by Kaposi in 1875, who observed recurrent delirium in several SLE patients (2). Similarly, Osler, in 1895, and Libman and Sacks, in 1924, noted the CNS manifestations of recurrent delirium, convulsions, nuchal rigidity, and paralysis (3, 4). Subsequently, other major reviews describing and characterizing the CNS manifestations of SLE have been offered, most notably by Harvey in 1954 (5), Johnson and Richardson in 1968 (6), and Dubois in 1974 (1). Although in the initial descriptions of SLE, CNS involvement was considered quite rare, more recent observations have indicated that the CNS manifestations are diverse and frequently contribute to SLE-related death.

Classification

The wide spectrum of CNS disorders can be divided into two broad clinical categories: neurologic and psychiatric (1, 5–7). Neurologic manifestations include:

- Seizures—grand mal, petit mal, psychomotor, or focal—in the presence or absence of renal disease.
- Cranial nerve dysfunction, the most common

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TABLE 1
Prevalence of Individual CNS Manifestations in SLE Patients

CNS manifestations	Prevalence (%)
Psychiatric dysfunction	12–71
Seizures	5–42
Cranial nerve disorders	5–42
Pareses	4–25
Movement disorders	2–5

initial symptoms being pupillary, visual, or extraocular eye movement disorders (cranial nerves II, III, IV, VI); less frequent initial symptoms include trigeminal neuropathy with facial hypoesthesia (cranial nerve V), Bell's palsy (cranial nerve VII), or nystagmus and vertigo (cranial nerve VIII) in isolation or within the context of other symptoms involving the brainstem.

- Movement disorders with symptoms of cerebellar ataxia, tremor, chorea, or athetosis.
- Pareses; common symptoms are monoparesis, hemiparesis, or quadriparesis associated with symptoms of aphasias, apraxias, or cranial nerve deficits localizing a major cerebrovascular insult to various parts of the cortex, internal capsule, or brainstem. Initially, paraparesis usually appears as a form of transverse myelitis.
- Miscellaneous disorders: intractable headache, aseptic meningitis, pseudotumor cerebri (in the presence or absence of corticosteroids), or coma as the initial or final symptom of a variety of major CNS insults.

Psychiatric manifestations include:

- Organic brain syndrome with symptoms of impaired orientation, recall, retention, or affectual lability.
- Depressive affective syndrome with a low mood and three or more additional typical depressive symptoms, such as fatigue, anorexia, and weight loss.
- Manic affective syndrome with three or more typical manic symptoms, such as hyperactivity, pressure of speech, or flight of ideas.
- Psychosis/schizophreniform syndrome with delusions, hallucinations, or catatonic behavior.
- Mixed syndromes displaying combinations of these symptoms, or miscellaneous psychiatric syndromes, including a variety of personality disorders and nonspecific disorders of consciousness such as delirium.

Kassan and Lockshin (8) have stressed the importance of strict definition and classification of SLE-CNS disease. In their system of classification, a CNS event should be defined according to its major clinical manifestation, such as seizure or motor or movement disorder, and further defined in terms of the presence or absence of confounding non-CNS abnormalities, such as hypertension or renal failure, and the presence or absence of CNS laboratory phenomena. The extent of CNS disease can then be quantitated, ranging from normal to impaired to incapacitated. In addition, the chronology of the disease can also be characterized as episodic, remittent, sustained, or progressive. In Part 2 it will become apparent that CNS manifestations can also be classified by primary molecular pathologic etiologies.

Epidemiology

The annual incidence of SLE ranges from 3 to 27.1/100,000, depending on the population studied. The prevalence of the disease is 50.8/100,000 in the general population. The prevalence of SLE is higher in the female population and in particular in the black female population, with prevalences of 1/700 and 1/245, respectively (9). The reported prevalence of CNS manifestations in SLE ranges from 25% to 75%. The prevalences of individual CNS manifestations (1, 6, 7) are also wide (Table 1).

The prevalence of individual psychiatric disorders in SLE is 12%–59% for patients with psychosis/schizophreniform syndrome, 31% for patients with the depressive/manic syndrome, and 15% for those with organic mental syndrome. Thus, psychiatric disorders as a whole are one of the most common CNS manifestations (Table 1). They vary greatly, from isolated symptoms not causing functional disability to illness causing severe psychosocial impairment necessitating hospitalization. It has been noted that 63% of CNS manifestations either precede the diagnosis of SLE or occur within the first year of diagnosis (7).

Pathology

The first pathologic examination of the CNS of SLE patients was undertaken by Kaposi in 1872 (10). These observations were remarkable only for gross brain atrophy. In 1936 Jarcho (11) was the first to report occluded small vessels with microinfarcts in the brain of an SLE patient. Incidentally, this patient had no clinical neurologic abnormalities. Subsequently, many authors have reported small brain infarcts associated with small arterial, arteriolar, or venous occlusions.

Johnson and Richardson (6) in 1968 found gross brain pathology in almost 50% of the specimens studied, consisting of intracerebral pontine or subpial hemorrhages as well as old and new infarcts. However, about 80% of the specimens examined had microscopic pathology: microinfarcts, increased pericapillary microglia, fibrinoid degeneration, hyalinization of arterioles, and fibrin thrombi. The frequent occurrence of microinfarcts implied that CNS-SLE disease primarily affected small vessels. Although at one time SLE-CNS disease was postulated to be an inflammatory process, true arteritis, that is, inflammatory cells within the cerebral vasculature, was rarely detected in these patients. However, perivascular infiltrates of inflammatory cells were frequently detected.

This classic study highlighted several important points on the molecular etiology of CNS disease (the focus of Part 2). First, there is no single typical or pathognomonic SLE lesion in the brain comparable to the wire loop lesion in the kidney. Second, the idea of true SLE cerebral arteritis (cerebritis) should be dispelled. Third, and most important, the constellation of CNS manifestations, particularly those with psychotic/schizophreniform syndromes, defied pathoanatomic correlation. Furthermore, whereas most SLE patients had CNS micropathology, not all SLE patients had clinically detectable neurologic abnormalities.

Another pathologic study, by Ellis and Verity (12) in 1979, found that the most common CNS pathologies included vasculopathy (65%), infarction (44%), hemorrhage (42%), and infection (28%). Common microvascular lesions included hyalinization of the meningeal, subcortical, and cortical arterioles, as well as perivascular lymphocytosis and endothelial proliferation. Ellis and Verity confirmed Johnson and Richardson's observations that true vasculitis was indeed rare. Microinfarcts in the superficial convexity of the cortex were most commonly found in the parietal and temporal lobes. Large infarcts were usually distributed in the distribution of the middle cerebral artery. In this study, cranial nerve palsies could be correlated with microinfarcts 72% of the time, whereas hemiparesis could be correlated with either microinfarcts, subarachnoid hemorrhage, or intracerebral hemorrhage approximately 50% of the time.

Diagnosis

SLE in general is rather difficult to diagnose, because there is no classic pattern and because the initial complaint is exceedingly variable (1). The American Rheumatological Association has proposed as preliminary criteria for identification of SLE the presence of 4 of the following 14 manifestations: facial erythema (butterfly rash); discoid lupus (erythematous raised patches); Raynaud's phenomenon; alopecia; photosensitivity; oral or nasopharyngeal ulceration; arthritis without deformity; LE (lupus erythematosus) cells; chronic false-positive serologic test for syphilis; profuse proteinuria; cellular casts; pleuritis and/or pericarditis; CNS manifestations; hemolytic anemia, leukopenia, and/or thrombocytopenia.

TABLE 2

Sensitivity of Tests Used to Diagnose SLE-CNS Disease

Test	Sensitivity (%)
Serum	
Antineuronal antibodies	41–92
Decreased complement	35–55
Warm reactive IgG	42
Synaptic vesicle protein inhibiting factor	
CNS	43
Psychiatric	100
CSF	
Increased cGMP	50
Increased protein	24–50
Increased DNA	64
Increased IgG	69–75
Increased lymphocytotoxic activity	73
Increased immune complexes	97
Ancillary studies	
CAT scan	75
EEG	71–89
Brain scan	8–100
MRI	86
Evoked potentials	93

Currently, the most accurate diagnostic laboratory test is the presence of antinuclear antibodies (ANA) in high titers. This test is 90%–98% sensitive and 86% specific. Recently it has been demonstrated that DNA binding capacity may detect some ANA-negative patients (13).

In general, the diagnosis of SLE-CNS disease is qualitative and descriptive. The variety of laboratory, neurophysiologic, and neuroradiologic tests currently used, their sensitivities, and evaluations of their clinical utility are discussed below. The current tests include measurements performed on patient serum or cerebrospinal fluid (CSF) and ancillary evaluations utilizing CAT scan, magnetic resonance imaging (MRI), electroencephalogram (EEG), and evoked potentials (EPs).

TABLE 3

Sensitivity and Specificity of Serum SVPK Inhibition Assay for SLE or SLE Patient Subsets in Sample Populations

Disease in population of interest	Sensitivity (%)	Specificity (%)
SLE-CNS in general population	45.8	85.8
SLE-psychiatric in general population	100.0	85.8
SLE-CNS in SLE population	45.8	89.7
SLE-psychiatric in SLE population	100.0	88.8
SLE-CNS in CNS disease population	45.8	93.8
SLE-psychiatric in psychiatric population	100.0	87.5

TABLE 4

Disease Entities of Patients with Serum SVPK Inhibition

Disease	Total	SVPK inhibition	Frequency (%)	Mean % serum (inhibition ± SEM)
Inflammatory	31	6	19.4	4.7 ± 1.8
Osteoarthritis	8	4	50.0	17.3 ± 6.3
Neuropsychiatric				
Depression	6	1	16.0	13.3 ± 12.4
Amyotropic lateral sclerosis	5	1	20.0	12.6 ± 11.8
Autoimmune				
Graves' disease	2	2	100.0	29.2 ± 3.1
Myasthenia gravis	2	1	50.0	20.0 ± 14.3
Sjogren's disease	1	1	100.0	19.0 ± 0.0
Rheumatoid arthritis	61	8	13.0	3.6 ± 1.3
Suspected rheumatoid arthritis	6	1	16.0	7.0 ± 6.5
Progressive systemic sclerosis	9	1	11.1	2.3 ± 2.2
Suspected systemic lupus erythematosus	16	7	37.5	13.1 ± 4.1
Systemic lupus erythematosus (total)	63	15	23.0	12.5 ± 3.4
SLE without active CNS	39	4	10.3	1.9 ± 0.95
SLE with active CNS	24	11	45.8	26.1 ± 1.5
SLE with active psychiatric disease	9	9	100.0	62.9 ± 9.3

Adapted from (19).

Serum Assays. The sensitivity of detecting serum antineuronal antibodies in SLE-CNS patients varies greatly from one laboratory to another (Table 2). This may be attributed to the different techniques and definitions of CNS disease employed by the different authors (14, 15). The specificity of the assays was not always great. Antineuronal antibodies were detected in approximately 25% of SLE patients without CNS disease as well as in 25% of rheumatoid arthritis patients.

Although depressed serum complement was detected in 35%–55% of SLE-CNS patients (Table 2) (16, 17), no statistical difference was found between SLE patients with or without CNS manifestations.

Detection of increased warm reactive antibodies in SLE-CNS patients had a relatively high sensitivity for patients with diffuse, yet not focal or psychotic disease (18) (Table 2). However, none of the patients in that study had psychiatric manifestations. By screening sera from a large patient population with an array of heterogeneous, autoimmune, inflammatory, and CNS diseases it was found that SLE patients with the CNS manifestations of schizophreniform syndrome/psychosis or depression had serum factors that inhibited in vitro brain synaptic vesicle protein kinase (SVPK) activity (Table 2) (19). Synaptic vesicles are axon terminal organelles that store neurotransmitter. Activation of SVPK activity has been implicated in neurotransmitter release (20). SLE patients with neuropsychiatric diseases were accurately detected in a heterogeneous patient and control population as well as a heterogeneous SLE and neuropsychiatric patient population (for sensitivities and specificities see Table 3). Although patients with other diseases had serum SVPK inhibition, neither the extent nor the frequency of inhibition approached that of SLE-neuropsychiatric patients (Table 4). Detailed analysis of the serum of an SLE patient with psychosis revealed that the IgG fraction of serum retained the SVPK inhibitory activity, whereas the remainder of the serum did not (19).

It was also found that SLE patients with active CNS disease have antisynaptic vesicle IgG antibodies as detected by radioimmunoassay (21) (Table 5). Sera from control patients and SLE patients without CNS manifestations did not have significant levels of antisynaptic vesicle IgG antibodies. SLE patients with inactive CNS disease, including cerebrovascular accident and seizures, had serum antisynaptic IgG concentrations significantly higher than that found in control serum or SLE disease without CNS manifestations. Patients with active CNS disease had a mean synaptic vesicle IgG serum antibody titer significantly higher than that of SLE patients with inactive CNS manifestations (Table 5). SLE patients with depression had the highest concentration of synaptic vesicle antibodies (Table 5). A high correlation was found between concentration of serum antisynaptic vesicle IgG levels and serum SVPK inhibition.

Thus, these studies demonstrated that SLE patients with psychiatric disease had serum factors capable of inhibiting in vitro synaptic vesicle enzymatic activity, which is typically associated with neurotransmitter release. This same group of patients also had high levels of radioimmunoassay-detectable brain antisynaptic vesicle IgG antibodies. Furthermore, the serum IgG of one patient was capable of inhibiting SVPK. It is thus suggestive that the factor possessing SVPK inhibitory activity in SLE patients is an IgG autoantibody. Part 2 of this study offers speculation on the possible role of these anti-SVPK IgGs in the etiology of CNS disease.

CSF Assays. Routine analysis of SLE-CNS CSF typically reveals a lack of pleocytosis and protein elevation. The sensitivity of laboratory tests employing lumbar puncture and analysis of CSF (22–25) range from 24% to 97% (Table 2). Many of these tests, with the exception of the IgG assay, have not been found to be specific. Increased cGMP, for example, has also been found in patients with cerebrovascular accidents, spinal cord tumors, and other neurologic entities.

One of the most promising of the CSF tests is the detection of increased CSF immune complexes (25). The test has a sensitivity of 97% as well as a very high specificity. Only 8% of non-SLE-CNS patients, 4% of multiple sclerosis patients, and 5% of patients with a variety of other non-SLE diseases had increased CSF immune complexes. The CNS-SLE manifestations in this study, however, did not include most psychiatric manifestations of SLE.

In many of the CSF assays studied, only the percent of detected CNS-SLE patients was recorded. It is unknown what the specificities of many of these tests are, and thus their potential utility is difficult to assess.

Ancillary Diagnostic Studies. Gonzales-Scarano et al (26) demonstrated that approximately 75% of SLE-CNS patients had abnormal CT scans (Table 2), consisting of cortical sulcal enlargement particularly prominent in patients with either psychosis or dementia. These CT findings were nonspecific and are also quite common in patients with Alzheimer's disease or alcohol abuse. Infarcts and intracranial hemorrhages were accurately detected by CT. Many patients with SLE-CNS disease, however, have normal brain CT scans (26).

Nonspecific EEG abnormalities with diffuse slowing were found in 71%–84% of SLE-CNS patients studied (27, 28). These changes were in no way diagnostic or sensitive, in that some SLE patients without CNS disease had grossly abnormal EEGs, whereas some patients with severe CNS involvement had normal EEG patterns. Other ancillary procedures, such as brain scans, MRI, and evoked potential (28–30), with varying reports on sensitivities (Table 2) are currently under investigation for detection of SLE-CNS disease.

TABLE 5

Mean Antisynaptic Vesicle IgG Concentration and Percent SVPK Inhibition of Four Groups of Patients

Group	N	Mean serum anti-sv IgG (±SEM) (ng/μg sv/μL serum)	Mean % SVPK inhibition (±SEM)
Controls	6	0.22 ± (0.21)	0
SLE − CNS	4	0.35 ± (0.30)	7.5 ± (3.2)
SLE + inactive CNS	4	3.2 ± (0.65)	25 ± (21.7)
SLE + active CNS			
(total)	13	7.5 ± (4.6)	41.5 ± (11.6)
Schizophrenia	2	0.85 ± (0.16)	100 ± (0)
Depression	6	14.81 ± (9.0)	52.8 ± (15)
Miscellaneous CNS	5	1.45 ± (0.46)	4.6 ± (4.1)

Purified synaptic vesicles were prepared from gray matter of bovine brain cerebral cortex. RIA performed by incubating 100 μL of 1:10 serum dilution with 100 μg synaptic vesicles for 8 hr at 25°C in total volume of 500 μL phosphate buffer saline, pH 7.4. Vesicles and bound antibodies were centrifuged at 2000 × *g* for 10 min. Pellet was washed with PBS buffer and recentrifuged at 2000 × *g* for 10 min; this step was repeated twice. Vesicle-antibody pellet was then resuspended in PBS buffer and incubated with 7.8 μg ^{125}I protein A (hot and cold mixture) (S.A. 89.0 μCi/μg) for 8 hr in a total volume of 500 μL. Vesicle-IgG-protein A complex was centrifuged at 2000 × *g* for 10 min. Pellet was washed and treated as above. Radioactivity of pellets was determined. Nonspecific ^{125}I protein A binding was determined by performing similar incubations with control sera. Mean control serum ^{125}I binding was subtracted from all values to calculate specific binding. Antisynaptic vesicle IgG concentration was calculated based on assumption of 1:1 binding of protein A and IgG.

Therapy

The mainstay of SLE therapy in the absence of CNS disease consists of corticosteroids, immunosuppressive therapy including azathiaprine, cyclophosphamide, and—rarely—plasmaphoresis (31). Occasionally, functional psychosis may be precipitated in SLE patients by an increase in corticosteroid dosage (32). These patients usually respond to decreases in steroid dosage and administration of psychoactive drugs. Most neuropsychiatric episodes (82%), however, occur while the patients are either on no or low-dose corticosteroids (32). In one study only a small number of patients (2 of 140) had what could retrospectively be identified as drug-induced psychosis (32).

The initial recommended treatment for SLE-CNS manifestations and exacerbations is an increase in corticosteroid dosage. Dubois et al and other investigators have reported that large doses of corticosteroids produced improvement in CNS manifestations within 2 weeks (33). This point, however, is controversial. Others maintain that there is no evidence that therapy with large doses of steroids are beneficial and that treatment with lower doses of corticosteroids are just as effective as massive doses (32).

Immunosuppressive drugs such as azathioprine and cyclophosphamide are occasionally used when the CNS manifestations are not controlled by high-dose steroids or when there are severe corticosteroid-induced complications.

Plasmaphoresis is being increasingly used in the treatment of SLE-CNS. Favorable responses can be anticipated if there are high levels of serum immune complexes and antibodies to double-stranded DNA and high levels of CSF immune complexes (34). In a report by Evans et al, a patient with schizoaffective syndrome unresponsive to 200 mg/day of prednisolone underwent plasma exchange with marked improvement in function as well as a corresponding decrease in immune complexes and antineuronal antibody titers (35). In other reports (34), plasmaphoresis alone leads to only brief improvement followed by a course of clinical deterioration within one month. Plasmaphoresis combined with corticosteroids and cyclophosphamide usually leads to the most favorable outcome. Rossen et al described a patient with renal and CNS involvement in whom treatment with cyclophosphamide, prednisolone, and repeated plasma exchange led to neurologic remission and reduction of circulating immune complexes (34).

In addition to these treatments, thought and affective disorders of SLE patients, when they arise, are treated with supplementary agents employed for the treatment of patients with these symptoms in the absence of SLE. Patients with depression are treated with a variety of benzodiazepines. Recently clonazepam, an anticonvulsant drug, was found to be efficacious in the treatment of recurrent symptoms of depression and anxiety (36). Patients with psychotic symptoms are treated with some success by the addition of Thorazine or Haldol.

New promising experimental therapy for SLE in general, which may extend to SLE-CNS disorders, includes antibody and hormonal modulation, including administration of monoclonal antibodies or cyproterone, an antigonotrophic drug, or removal of OKT8 cells (37–39).

Conclusion

The CNS manifestations of SLE are diverse and account for a high proportion of morbidity and mortality within the SLE patient population. Diagnosis of SLE-CNS may be difficult in the presence of confounding factors such as concomitant steroid therapy or if the CNS disease is the initial manifestation of SLE. A variety of laboratory and radiologic and physiologic tests have been devised to aid detection of SLE-CNS, each with varying sensitivities and specificities. Some are more specific for psychiatric or neurologic symptoms or for those symptoms attributable to an obvious radiologically detectable CNS insult. Diagnosis must be made clinically within the context of carefully chosen ancillary procedures. Current therapy for the most part curtails CNS symptoms, offering occasional and infrequent remission. It is hoped that experimental therapy emphasizing the molecular pathology of SLE, currently under trial, may offer better control of the disease. The presence of a pathoanatomic correlation with some clinical symptoms and not with others, as well as the presence of specific brain enzyme inhibiting factors and/or autoantibodies in some patients and not in others, provides clues to the formulation of a unifying hypothesis that takes into account a multiplicity of molecular dysfunctions capable of accounting for the diversity of CNS-SLE disease expression. This analysis is taken up in Part 2.

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Mezlocillin versus Doxycycline in the Treatment of Acute Salpingitis

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Abstract

Twenty-four women with laparoscopically documented salpingitis were randomly selected for double-blind intravenous treatment with either mezlocillin or doxycycline. Mean age, parity, gravidity, and severity of the disease were similar in both groups. Eleven of the 13 women (85%) treated with mezlocillin and 8 of the 11 women (73%) treated with doxycycline had positive genital cultures. The specimens were obtained either from the uterine cervix or the peritoneal cavity.

The microorganisms recovered in both groups included *Neisseria gonorrhoeae, Chlamydia trachomatis,* and other bacteria, in apparently random distribution not related to either medication.

Oral temperatures, sedimentation rates, leukocyte counts, and well-being of patients treated with either antibiotic improved within three days. Analysis of these parameters did not reveal any statistically significant differences. It is concluded that our patients with salpingitis responded similarly to intravenous treatment with either mezlocillin or doxycycline and subsequently improved without any complications or adverse side effects.

The optimal antibiotic treatment of acute salpingitis is controversial (1). Most authors agree that antibiotic treatment is preferably administered in a hospital, intravenously. Ambulatory treatment with either oral or intramuscular antibiotics seems to yield unsatisfactory results (2). It is unclear whether a single antibiotic agent or a combination of several antibiotics provides better results (1, 3).

Additional factors which interfere with the unequivocal determination of an optimal antibiotic regimen in the treatment of acute salpingitis include the variety of new antibiotics with different absorption, mechanism of action, bactericidal spectrum, side effects, and price. Treatment protocols often include multiple medications (1), making the effectiveness of each agent difficult to assess. (4). Temporal changes in bacterial species recovered from patients with acute salpingitis, different culture techniques, the appearance of resistant strains, and an increasing awareness of the importance of microorganisms such as *Chlamydia trachomatis* (5) and *Ureaplasma urealyticum* (6) in the pathogenesis of acute salpingitis dictate frequent reevaluation of current treatment regimens.

A precise definition of salpingitis requires laparoscopy and direct cultures from the fallopian tubes and the cul-de-sac (1). Some clinical studies performed without diagnostic laparoscopies failed to fulfill these requirements and thus introduced inaccuracies in interpretation of the results. To add ambiguity to the diagnostic dilemma, salpingitis may vary in severity and clinically the symptomatology may be incomplete (7).

We have recently reported the use of mezlo-

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TABLE 1

Characteristics of 24 Patients with Acute Salpingitis by Drug Treatment (Mezlocillin or Doxycycline)

	Treated with mezlocillin (N = 13)	Treated with doxycycline (N = 11)
Age (yrs)	25.5 ± 4.6	23.1 ± 4.7
Gravidity (no.)	2.4 ± 1.7	2.6 ± 1.4
Parity (no.)	1.9 ± 1.1	1.7 ± 1.0
Laparoscopic staging of salpingitis		
Mild (no.)	4	3
Moderate (no.)	6	5
Severe (no.)	3	3

$P > 0.05$ (NS) for age, gravidity, parity, and laparoscopic staging of salpingitis.

cillin, a new acylureide penicillin, in the treatment of acute salpingitis. Mezlocillin was found to be effective in the treatment of 26 of 28 women with laparoscopically documented salpingitis (8).

The purpose of this study was to prospectively evaluate, in a double-blind protocol, mezlocillin versus doxycycline in the treatment of laparoscopically documented salpingitis.

Materials and Methods

Twenty-seven women underwent diagnostic laparoscopy with suspected acute salpingitis from February 1984 to March 1985. One woman was found to have an inflamed Meckel's diverticulum and two had acute appendicitis. None of the remaining 24 women with salpingitis were either pregnant or allergic to penicillin. A detailed informed consent was obtained from all patients.

Clinically, all the women had at least three of the following symptomatic criteria: lower abdominal pain, rebound or guarding on palpation of the lower abdomen, cervical tenderness on pelvic bimanual examination, elevated temperature of more than 38° C, purulent vaginal or cervical discharge, white blood cell count of more than 12,000/cu mm leukocytes or elevated erythrocyte sedimentation rate of more than 15 mm/hr. Blood samples were cultured for *Neisseria gonorrhoeae* aerobic and anaerobic microorganisms. Cervical and endometrial swab cultures for *N. gonorrhoeae, C. trachomatis* (McCoy cell culture) (5), and *Mycoplasma hominis* (6) were also obtained on admission.

The patients were hydrated prior to laparoscopy with intravenous infusion of lactated Ringer's solution for a few hours. Oral and rectal temperature measurements were recorded every eight hours.

Closed laparoscopy was performed with standard equipment. The peritoneal cavity was insufflated with carbon dioxide and subumbilical and suprapubic incisions were performed to approach the pelvic cavity. The vermiform appendix, the hepatic portal area, the bowels, the domes of the liver, and the diaphragm were routinely inspected during laparoscopy. Salpingitis was staged as mild, moderate, or severe according to the criteria established by Hager et al (7). Bacterial cultures and Gram-stained smears were obtained from the fimbrial end of both fallopian tubes and from the cul-de-sac. Four patients had an intrauterine device (IUD) in place; the IUD was retrieved and cultured at the time of laparoscopy.

Once salpingitis was laparoscopically documented, intravenous antibiotic treatment was instituted. Mezlocillin (4 gm every six hours) or doxycycline (100 mg every 12 hours) were randomly and blindly selected. Two placebo bags with normal saline were alternately administered with doxycycline every 12 hours. Intravenous infusion bags with the antibiotics were randomly coded and only the director of the pharmacy had access to the key list. Intravenous treatment was discontinued after 3–5 days and the patients were discharged from the hospital on a regimen of oral ampicillin 2 gm/day until they became asymptomatic and erythrocyte sedimentation rate declined below 15 mm/hr. Patients who did not respond to three days of either antibiotic were subjected to reevaluation and addition of a second antibiotic agent.

Treatment was also reevaluated whenever the cultured microorganisms were found to be resistant in vitro to both mezlocillin and doxycycline. Erythrocyte sedimentation rate, complete blood count, and routine biochemistry blood profile (SMA-24) were obtained daily.

Age, gravidity, parity, temperature measurements, hemogloblin, hematocrit levels, presence of peritoneal signs, presence of cervical tenderness, and staging of salpingitis of patients treated with mezlocillin were compared to those of women treated with doxycycline using Student *t* and Fisher's exact tests.

Results

Twenty-four women with laparoscopically documented salpingitis were treated with either mezlocillin or doxycycline. Thirteen patients received mezlocillin and eleven women received doxycycline. Mean age, gravidity, parity, and laparoscopic staging of salpingitis were similar in

TABLE 2

Microorganisms Cultured from Patients with Acute Salpingitis Later Treated with Either Mezlocillin or Doxycycline

Mezlocillin (N = 13)			Doxycycline (N = 11)		
Endocervix and/or endometrium	Fallopian tubes and/or cul-de-sac	Other site	Endocervix and/or endometrium	Fallopian tubes and/or cul-de-sac	Other site
Peptococcus sp. Peptostreptococcus sp. Lactobacillus sp.	—	—	Streptococcus sp. Peptostreptococcus sp.	—	IUD: Veillonella sp. Peptococcus sp.
E. coli β-hemolytic Streptococcus		Urine & IUD: E. coli	N. gonorrhoeae Veillonella sp.	—	Urine: Strep. viridans
C. trachomatis	—	—	C. trachomatis Strep. viridans	C. trachomatis	—
—	—	—	Peptostreptococcus sp.	—	—
N. gonorrhoeae E. coli K. pneumoniae	—	—	Peptostreptococcus Staph. epidermidis	—	IUD: S. epidermidis K. pneumoniae
N. gonorrhoeae	—	—	—	—	—
C. trachomatis	—	—	C. trachomatis	—	Urine: E. coli
—	—	—	N. gonorrhoeae	N. gonorrhoeae	—
β-hemolytic Streptococcus	—	Blood: Micrococcus sp.	Staph. epidermidis	—	Urine: E. coli
B. fragilis	—	—	—	—	—
β-hemolytic Streptococcus	—	IUD: β-hemolytic Streptococcus	C. trachomatis	— —	—
N. gonorrhoeae Peptostreptococcus sp.	—	—			
N. gonorrhoeae B. fragilis Peptostreptococcus sp.	N. gonorrhoeae	—			

both groups (Table 1). Eleven (85%) of the patients treated with mezlocillin and eight of the patients treated with doxycycline (73%) had been culture positive on admission. One patient treated with mezlocillin and two patients treated with doxycycline had positive cultures from the peritoneal fluid. The different microorganisms had an apparently scattered distribution between the two groups (Table 2).

Both groups defervesced during a three-day hospital stay. Repeated Student *t*-test of temperature taken at 8-hr intervals did not reveal any significant differences between the two groups of patients. Both groups had moderately elevated leukocyte counts (between approximately 10,000 to 20,000/cu mm). On day three of intravenous antibiotic treatment, both groups had been leukocyte counts less than 10,000/cu mm. Statistical analysis did not reveal any differences between the two groups.

Daily mean sedimentation rates of women with salpingitis treated with either mezlocillin or doxycycline increased shortly after admission, then decreased a few days later in both groups. Standard variations were large and statistical analysis did not reveal any differences between the two treatment groups. Routine chemical laboratory profile (Sequential Multi-Analyzer, SMA-24) subjected to paired Student *t*-tests did not reveal any differences between the two treatment groups.

All patients were discharged to return home on a regimen of oral ampicillin 2 gm/day for an additional week, unless *C. trachomatis* was recovered from one of the genital cultures. Then, the women were instructed to change the oral antibiotic to doxycycline 200 mg/day. Repeated cervical cultures revealed normal vaginal flora. Two patients treated with mezlocillin returned with abdominal pains and fever, in two weeks and one month after laparoscopy. The first patient was readmitted for repeat intravenous antibiotic treatment with penicillin, gentamicin, and clindamycin and subsequently improved. The second woman responded to oral administration of ampicillin 2 gm/day and metronidazole 2 gm/day for an additional 2 weeks, with clinical and laboratory improvement. Two women treated with doxycycline had only partial resolution and required a longer treatment with oral ampicillin 2 gm/day and metronidazole 2 gm/day for an additional two weeks, with clinical and laboratory improvement. Repeated cervical cultures revealed normal vaginal flora.

All patients were followed up for six months after laparoscopy with pelvic examinations and at least two cervical cultures.

Discussion

The prospective, double-blind design of this study provided an optimal investigative tool to compare the efficacy of mezlocillin versus doxycycline in the treatment of acute salpingitis. Laparoscopy combined with tubal, peritoneal, urine, blood, and cervical cultures and application of common diagnostic criteria of salpingitis (7) were utilized to establish the diagnosis of acute salpingitis. Based on this protocol, three women were excluded from the study because of other abdominal pathologies. This number is consistent with the original report of Jacobson and Westrom (9), who found that 15% of patients suspected to have acute salpingitis had other diseases such as appendicitis, endometriosis, ectopic pregnancies, and benign ovarian cysts.

Single antibiotic agents were evaluated in this study to avoid the uncertain interpretation of results obtained from administration of more than one antibiotic. Mezlocillin was selected to be the first single antibiotic agent because of its broader spectrum (10). The use of such an antibiotic agent may potentially substitute for the multiple-antibiotic combination therapy necessary to answer the polymicrobial etiology of salpingitis (11) and reduce direct costs. Doxycycline was selected to be the second antibiotic because it fulfilled these requirements and provided additional coverage for *C. trachomatis* and the mycoplasmas (12). Since this study was first conceived, preliminary reports have appeared on the efficacy of mezlocillin against *C. trachomatis* (13). Two of our patients with cultures positive for *C. trachomatis* responded to mezlocillin treatment. This observation deserves further in vivo and in vitro studies to establish the efficacy of third-generation penicillins against *C. trachomatis*.

Four women (17%) had intrauterine contraceptive devices and acute salpingitis. Three devices grew only a single pathogen and one device cultured two microorganisms (Table 2). Cervical cultures obtained from the same patients yielded three or more microorganisms, including the same pathogens recovered from the device. This observation supports the polymicrobial, synergistic nature of acute salpingitis in the presence of an infected nidus such as an IUD (14).

Eschenbach (15) reported that cultures of the peritoneal surfaces yielded lower rates of recovery of pathogens than the uterine cervix. The same phenomenon was observed in this study (Table 2). These results probably reflect patient selection bias, because only 25% of our patients had severe salpingitis (Table 1). Our microbiology laboratory, using the same culture techniques, recovered different species and numbers of microorganisms in laparoscopies of patients with salpingitis during a different time period (8). A changing study population can also explain these differences. Although a series of 24 patients may introduce type 2 error in interpretation of negative results (16), a beneficial effect of either antibiotic in a larger series would have been marginal at best.

Oral temperature, erythrocyte sedimentation rates, and leukocyte counts decreased to normal values on the third postoperative day in both groups. Statistical analysis did not reveal any significant differences between the two groups. It seems that in this series of patients with salpingitis, mezlocillin and doxycycline were equally effective when administered intravenously. These findings support the contention that a single broad-spectrum antibiotic administered intravenously may be effectively used in the initial treatment of acute salpingitis.

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No Association of Amyotrophic Lateral Sclerosis with Cancer

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Abstract

Five new cancers occurred among 347 patients with amyotrophic lateral sclerosis (ALS) (average age, 57 years) followed up in an ALS clinic for a mean of 2.5 years, an incidence of 0.57% per year. The incidence of cancer in the 55–59-year age group derived from the Connecticut Tumor Registry was 0.64% per year. Prior studies purporting to show an association between ALS and cancer were biased by selection of patients from populations with a high prevalence of cancer. Cancer incidence in ALS appears to be no different from cancer incidence in the general population. Cancer screening of ALS patients is unlikely to be more productive than cancer screening of age-matched patients without ALS.

Norris and Engel (1) reported a series of 130 consecutive patients with amyotrophic lateral sclerosis (ALS) of whom 13 (10%) had cancer. Three patients had lung cancer, two had colon cancer, and one each had astrocytoma, leukemia, seminoma, basal cell carcinoma, and cancer of the breast, thymus, and prostate. Twelve of the 13 neoplasms were present concurrently with ALS symptoms. Cancers were found in only 1.6% of unselected stroke patients during the same period. The authors concluded that ALS was associated with cancer.

We reviewed our experience with cancer in a large ALS clinic population to confirm this relationship and establish the value (if any) of cancer screening in newly diagnosed ALS patients.

Methods

The ALS clinic at The Mount Sinai Hospital, New York, is a multidisciplinary clinic dedicated to the care of ALS patients and to research in ALS. Patients are usually referred to the clinic after the diagnosis of ALS has been made elsewhere. Nearly all patients have had routine blood studies and chest films before coming to clinic; a minority have had extensive malignancy workups. Clinic policy is not to perform malignancy workups routinely. If signs or symptoms of cancer are present, appropriate tests are ordered.

Charts of the first 400 consecutive patients enrolled in clinic were reviewed for diagnoses of cancer. Fifty-three patients were excluded from further analysis because, in our opinion, they did not have ALS. Two of the non-ALS patients had cancer. Cancers among the 347 ALS patients were classified as "new" (cancer diagnosed after onset of neurologic symptoms) or "old" (cancer diagnosed prior to neurologic symptoms). All ALS-cancer patients had clinical evidence of lower-motor-neuron disease involving spinal-innervated musculature. Some also had bulbar disease, with weakness of muscles innervated by cranial nerves V, VII, X, and XII. Upper-motor-neuron disease was diagnosed in patients with pathologic reflexes or normal muscle stretch reflexes despite severe weakness.

The mean duration of neurologic symptoms for the 347 ALS patients evaluated in this study was 2.5 years as of the most recent clinic visit.

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† Deceased.

TABLE
Characteristics of 12 ALS Patients with Cancer

Case	ALS-cancer			ALS involvement‡	
	Age*	Interval†	Cancer type	UMN	Bulbar
1	51	+1	Lung	No	Yes
2	59	+0	Liposarcoma	No	Yes
3	70	+1	Lymphoma	Yes	No
4	51	+3	Lung	No	No
5	48	+1	Colon	Yes	Yes
6	55	−9	Colon	No	No
7	60	−5	Colon	No	No
8	71	−1, −20	Colon, melanoma	Yes	Yes
9	65	−3	Oral	No	No
10	69	−20	Breast	Yes	Yes
11	66	−4	Thyroid	Yes	No
12	66	−6	Testicle	No	Yes

* Age at onset on neurologic symptoms.

† Years elapsed between onset of neurologic symptoms and diagnosis of cancer. Negative number indicates cancer diagnosis before onset of neurologic symptoms.

‡ All ALS patients had typical findings of spinal muscular atrophy. UMN (upper motor neuron) and bulbar findings were also present in some patients.

Most surviving patients are still coming to clinic. Contact has been maintained, when possible, with homebound or institutionalized patients who can no longer attend clinic. Only 43 patients have been lost to follow-up.

Results

Of the first 347 ALS patients enrolled in the Mount Sinai ALS clinic, 12 had cancer or a history of cancer (Table). Five had "new" cancer diagnosed after onset of neurologic symptoms. The other 7 had "old" cancer diagnosed prior to onset of neurologic symptoms. All "old" cancer patients were successfully treated for cancer at least one year prior to onset of neurologic symptoms, and none has had recurrence.

The incidence of cancer in our ALS patients was 0.57% per year, based on 5 new cancers occurring in a group of 347 patients (average age 57 years) followed for a mean of 2.5 years from onset of neurologic symptoms. For comparison, the incidence of new cancers in the 55–59-year age group derived from the Connecticut Tumor Registry (2) was 0.64% per year.

Discussion

Our goals were to find out whether ALS patients are more prone to cancer than persons without ALS and what tests, if any, are indicated to screen for cancer in the newly diagnosed ALS patient. We directed our attention to "new" cancers occurring after onset of neurologic symptoms because annual cancer incidence can be calculated from these data, and because these are the cancers screened for by occult malignancy workups. We recorded 8 "old" cancers in 7 ALS patients, but since most of these tumors were successfully treated several years before onset of ALS and have not recurred, their relationship to ALS is highly speculative. We do not know the frequency of positive cancer histories in age-matched non-ALS patients.

The incidence of cancer in our ALS patients was not substantially different from the incidence of cancer reported by the Connecticut Tumor Registry (2). Possible biases decreasing our cancer incidence include the following: ALS patients not referred to us because of ongoing treatment in a cancer center, clinic patients lost to follow-up for the same reason, failure of patients to report a diagnosis of cancer, and incomplete perusal of our charts. Possible biases increasing our cancer incidence include the use of tests to identify occult cancers that otherwise might not have been found (as in patient 1) and our reporting of cancers that were diagnosed since the most recent cinic visit (as in patient 4).

Norris and Engel (1) reported a much higher rate of cancer than we found. One cannot compute an annual cancer incidence from their data, but their prevalence of cancer was 12/130 (9.2%), compared to the prevalence in our series of 5/347 (1.4%). All their cases were inpatients at the National Institutes of Health or at a major university hospital with a large cancer program. Over half of their ALS-cancer patients were originally hospitalized for cancer therapy. Their high rate can, therefore, be explained by the high rate of cancer in the population from which their patients were drawn.

This form of bias could also explain the finding by Shy and Silverstein (3) of 9 patients with cancer among 186 ALS patients having muscle biopsies, a rate of 4.8%. An appropriate control population (non-ALS patients having muscle biopsies at a university hospital) could easily have a 4.8% cancer rate or higher.

Brain et al (4) reported 11 patients with ALS and cancer. Selective referral of patients to this group because of their admittedly "known interest in carcinomatous neuromyopathy" explains this unexpected clustering.

Recent autopsy and death-registry data show no association between ALS and cancer. Analysis of all autopsies in Japan from 1964 to 1978 found the same cancer rate in persons with ALS as in persons with myocardial infarction, craniocervical injury, and pulmonary tuberculosis (5). A review of U.S. death-registry data by counties for five recent years found no correlation between ALS and five common neoplasms (6).

We conclude that cancer incidence in ALS is no different from cancer incidence in the general population, and that cancer screening of newly diagnosed ALS patients is unlikely to be more productive than cancer screening of age-matched persons without ALS.

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Discectomy following CT and MRI and Without Myelography

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Abstract

Two hundred patients with signs and symptoms of disc disease were evaluated preoperatively by conventional x-rays, computerized tomography, and magnetic resonance imaging. Magnetic resonance imaging was utilized instead of myelography to confirm the diagnosis and to rule out a spinal tumor. The operative findings in 160 lumbar laminotomies and 40 anterior cervical discectomies were predicted by and correlated with the neuroradiologic studies. Patient preference for the noninvasive imaging, avoidance of spinal tap, and zero complication rate was unanimous.

Two neurosurgeons in private practice at two community hospitals employed computerized tomography (CT) for initial neuroradiologic evaluation of patients with signs and symptoms of disc disease. Prior to surgery, every patient treated from 1979 through 1984 was hospitalized for a myelogram to confirm the diagnosis and to rule out a spinal tumor. In the 400 patients who underwent lumbar laminotomy and the 100 patients who underwent anterior cervical discectomy (1, 2), metrizamide myelography via lumbar puncture was frequently associated with some adverse symptomatology. Complaints of headache and nausea were recorded in more than half of the cases, and vomiting occurred primarily following cervical studies (20%). Severe confusion was noted in 6 of our patients, and there were 4 instances of grand mal seizure equally divided in lumbar and cervical studies, even though 100 mg of phenobarbital was regularly ordered as premedication. Beginning in 1985, patients with x-ray and CT evidence of disc disease preferentially underwent magnetic resonance imaging (MRI) at a private outpatient facility supervised by senior neuroradiologists.

Methods

Every patient who came to surgery had radicular pain unrelieved by conservative treatment for at least 6 months, or objective findings on neurologic examination, such as motor or reflex deficits. Lumbosacral or cervical spine x-rays were ordered as early as possible, but CT was reserved for those patients that did not respond to bed rest, traction, brace, analgesics, muscle relaxants, and antiinflammatory medication. When neurologic deficit dictated early intervention or the patient opted for discectomy to relieve intractable pain, MRI was employed as the second neuroradiologic study to confirm the diagnosis and to rule out a spinal tumor.

All of the CT images were formatted on a fourth-generation, high-resolution scanner (Technicare 2060), using both bone and soft tissue algorithms. Studies of the cervical spine were obtained with 2-mm contiguous sections through each suspected level with slices parallel to the plane of the intervertebral disc and perpendicular to the neural axis. The slices extended from the inferior aspect of the pedicle above the disc to the top of the pedicle below in order to en-

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compass the neural foramen, the plane of the disc, and the lateral recesses below the disc. Lumbar studies were performed with contiguous 4-mm axial slices parallel to the plane of the intervertebral disc and perpendicular to the neural axis at L3–4, L4–5, and L5–S1. Sections were made from the inferior margin of the pedicle above each intervertebral disc to the adjacent end plate below.

All of the MRI studies were produced by a permanent 3.0 kilogauss magnet (Fonar B2000). Cervical examinations were performed in the sagittal and axial projections using a wraparound surface coil. T1 weighted pulse sequences (TE 28, TR 666) were employed. The images were obtained with 4-mm thickness and 1-mm slice gap. The sagittal studies included the foramen magnum and extended through the cervicothoracic junction. Axial images were obtained through the symptomatic level and any other level disclosed as abnormal on the sagittal examination. Lumbar MRI studies were also performed in the sagittal and axial projections with 4-mm slice width and 1-mm slice gap. The sagittal studies included the conus medullaris and extended through the sacrum. Axial images were obtained pedicle to pedicle through the suspected level and any other level found to be abnormal on the sagittal examination. T1 weighted sequences (TE 28, TR 666) were again employed; but in some equivocal cases, a long echo sequence (TE 84, TR 2300) was added in the sagittal plane.

There were 108 women and 92 men in our series; the ages ranged from 19 to 68 years. A total of 160 lumbar laminotomies and 40 anterior cervical discectomies were performed over a 3-year period. Every patient was followed up for at least 6 months before being included in the statistical study.

Results

The diagnostic findings in our 160 patients with lumbar disc disease were consistent with a herniated nucleus pulposus: 82 at L5–S1, 61 at L4–5, 6 at L3–4, 11 at both L4–5 and L5–S1. Conventional x-rays rarely contributed to the diagnosis of a herniated lumbar disc. The lumbar CT scans in the illustrated case (Fig. 1) were highly accurate in identifying a herniated nucleus pulposus with nerve root compression. The MRI studies in the same case (Fig. 2) were primarily corroborative in confirming the disc herniation and excluding abnormalities of the conus medullaris or cauda equina. During the 3-year project, 9 patients with equivocal results on CT and MRI were also evaluated by iopamidol myelography, which was indeterminate; none of these patients came to surgery. In the 25 other patients who underwent laminectomy during the 3-year period, 17 instances of spinal stenosis, 5 cases of spondylolisthesis, and 3 tumors were correctly diagnosed by x-ray, CT, and MRI and without myelography. The neoplasms were an epidural plasmacytoma, a neurofibroma arising from an exiting nerve root, and a cauda equina neurilemoma.

The diagnostic findings in our 40 patients with cervical disc disease were consistent with spondylosis and osteophytic ridging in 32 cases, 8 at C4–5, 9 at C5–6, 9 at both C4–5 and C5–6, and 6 at both C5-6 and C6–7. Only 8 instances of acute herniation of disc material were documented, 2 at C4–5, 4 at C5–6, and 2 at C6–7. Conventional x-rays in the illustrated case (Fig. 3) diagnosed significant osteoarthritic changes. The CT scans in the same case (Fig. 4) demonstrated spondylitic ridges and disc protrusion compromising the spinal canal. The MRI studies in the same case (Fig. 5) exquisitely imaged the cervical spondylosis and spinal cord atrophy.

The findings at surgery in the 200 consecutive cases were entirely predicted by the two preoperative neuroradiologic studies. There were no false positives when CT alone demonstrated a lateral lumbar disc herniation in 8 patients or when MRI alone confirmed cervical disc disease associated with radiculopathy in 5 patients. Our experience with myelography as a second neuroradiologic examination was quite similar. The postoperative results were comparable to our previously published series of lumbar laminotomy and anterior cervical discectomy (1, 2). No complications of wound infection, intraoperative hemorrhage, cerebrospinal fluid fistula, discitis, or increased neurologic deficit were recorded. Twelve patients who remained symptomatic with sciatica were reevaluated by CT. Follow up MRI was performed on 3 patients who continued to complain of neck pain after their symptoms of cervical radiculitis were relieved. The only neuroradiologic findings were postoperative changes at the correct levels of exploration.

Discussion

Myelography utilizing positive-contrast media has been a generally approved diagnostic study for identification and precise localization of spinal lesions (3). DePalma and Rothman (4) continued to rely on clinical findings and inveighed

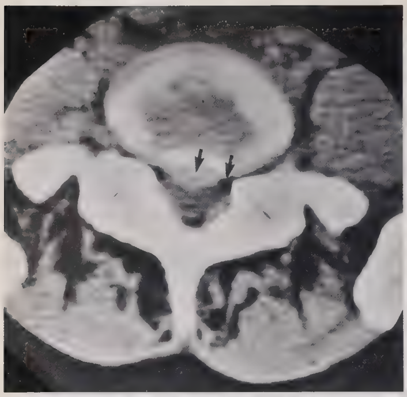
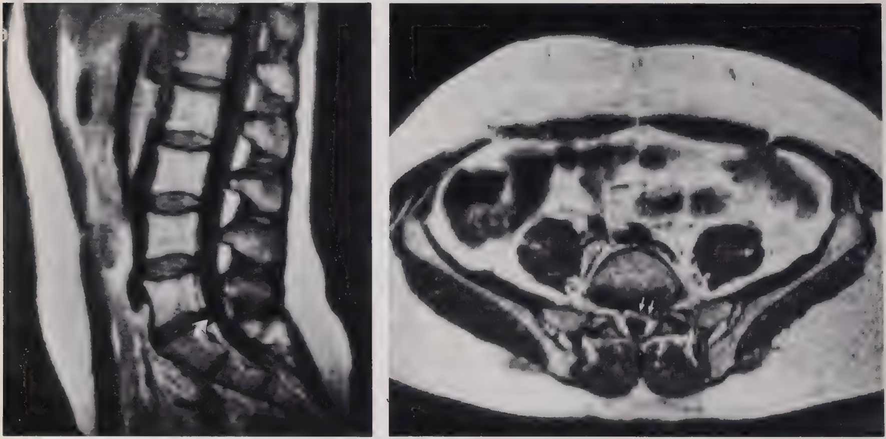
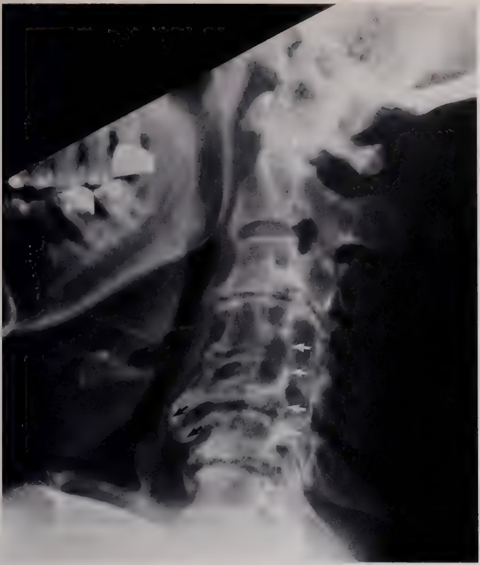


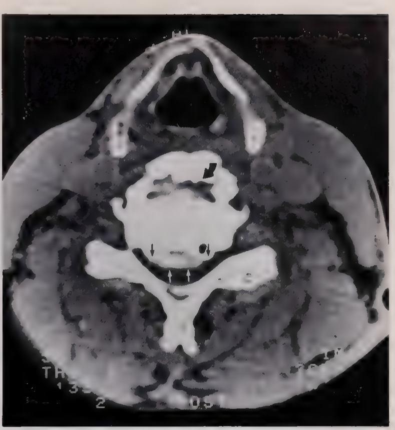
Fig. 1. Right Lumbar CT scan, soft tissue window. L5–S1 disc at level of midplane of disc; note disc herniation (arrows) slightly eccentric toward left side with compression of ventral aspect of dural sac. **Fig. 2.** Same patient. Lumbar MRI study (TE 28, TR 666). **A (below left)** sagittal section 4 mm left of midline, demonstrating herniation of disc material (arrow) at L5–S1 level with obliteration of ventral epidural fat and posterior displacement of thecal sac in central spinal canal. **B (below right)** axial section at L5–S1 level; note herniation of disc material centrally and laterally (arrows) with effacement of ventral epidural fat and posterior displacement of left S1 nerve root.



against routine use of an invasive procedure to establish the diagnosis and level of disc herniation. With the present availability of high-resolution scanners, many neurosurgeons and orthopedists consider CT the only necessary preoperative study for patients with lumbar disc disease (5). Prior to the introduction of MRI, the authors followed the neurosurgical training at The Mount Sinai Hospital and consistently performed a myelogram on every patient undergoing a spinal operation. Surgical decisions about herniated nucleus pulposus, segmental spondylosis, and degenerative disc disease continue to be based in our practice on two neuroradiologic studies. Equivocal findings of annular bulging at predicted levels, frank demonstration of disc herniation at levels without clinical correlation, or asymptomatic spinal stenosis were not treated by surgery.

Aqueous contrast materials have several advantages over oily agents for myelography; however, metrizamide studies are not innocuous procedures (6–8). Between 10% and 20% of patients may complain of anxiety, agitation, or nightmares during the first 24 hours following a metrizamide myelogram (9). More serious complications include nausea, emesis, meningeal irritation, fever, paresthesias, myoclonus, psychotic reactions, and seizures (8, 9). Premedication with phenobarbital, hydration with intravenous





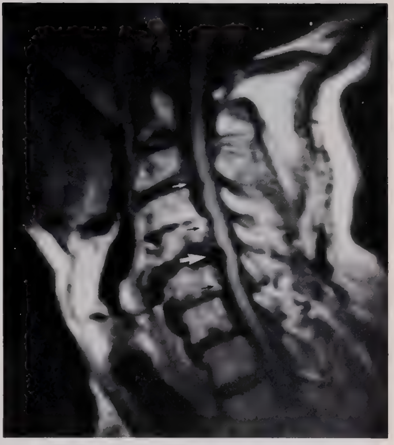


Fig. 3. Above Lateral view of cervical spine showing advanced degenerative spondylosis with disc space narrowing at C3–4, C4–5, C5–6, C6–7, and C7–T1. Spondylitic ridge formation encroaches on ventral spinal canal at C4–5 and C5–6 (white arrows), causing significant narrowing. Marked anterior osteophyte formation displaces esophagus (black arrows). **Fig. 4. Upper right** Same patient. Cervical CT scans, soft tissue window, 2-mm axial section through the C5–6 intervertebral disc, showing degenerative disease. Note intradiscal gas (curved black arrow), posterior herniation of calcified disc material (vertical white arrows) encroaching on ventral aspect of thecal sac, and osteophytic ridges (vertical black arrows) along posterior margin of inferior C5 end-plate. **Fig. 5. Lower right** Same patient. Cervical MRI study (TE 28, TR 666), sagittal section 4mm right of midline, showing diffuse spondylitic changes of cervical spine with ridge formation at C3–4, C4–5, and C6–7 (small arrows). Note herniated disc at C5–6 level (large arrow), projecting posteriorly and displacing ventral right lateral surface of spinal cord. Cervical cord is atrophic throughout.

fluids, and meticulous attention to myelographic technique to prevent direct spillage of metrizamide into the cranial cavity have not entirely eliminated these sequelae. Our own recent experience with iopamidol is too limited for comment.

MRI of the spine can characterize disc herniation with spatial resolution nearly comparable to CT and myelography (10). As with CT, multiplanar MRI is suited for demonstrating both central and lateral disc abnormalities; as with myelography, MRI has the capacity to image the entire spinal canal and thecal contents on sagittal, coronal, and axial views (11–14). CT allows for routine thinner section imaging than multiplanar MRI and is therefore less subject to volume averaging artefact. We were not willing to abandon CT for preoperative evaluation, since CT is better able to show degenerative bony changes along the vertebral end plates and facets and calcification within the annulus fibrosus and herniated disc fragments. Without CT correlation and extended training to interpret the findings of an innovative technology, MRI of asymptomatic arthritic changes in the bones and discs of the spine may appear to have surgical implications.

Summary

Even with the advance of CT scanning, myelography utilizing positive-contrast media remains a widely accepted preoperative diagnostic procedure for evaluation and localization of disc herniation. The complications of lumbar puncture and injection of metrizamide observed in 500 patients with disc disease induced two neurosurgeons in private practice to substitute MRI. Patient preference for the noninvasive imaging, avoidance of spinal tap, and zero complication rate was unanimous. In 200 consecutive patients who underwent discectomy, the neuroradiologic studies confirmed the clinical diagnosis and excluded a neoplasm. CT and MRI are ideally complementary examinations to evaluate both intradural and extradural abnormalities. The combination of conventional x-rays, CT, and MRI is sufficient and complete for the preoperative diagnosis of patients with suspected lumbar and cervical disc disease and makes conventional myelography and CT myelography unnecessary. The authors await further experience with MRI in tumors, trauma, stenosis, and congenital and acquired anomalies before suggesting that all spinal lesions can be adequately evaluated by noninvasive studies.

Acknowledgments

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Radiologic Findings in Möbius Syndrome

MATTHEW J. KUHN, M.D.

Abstract

The diagnosis of Möbius syndrome involves recognition of a variety of musculoskeletal anomalies, swallowing difficulty, and chronic aspiration pneumonia in a child with facial paralysis and external ophthalmoplegia. A typical case emphasizing the spectrum of radiologic findings observed in these patients is reported.

Möbius syndrome is a rare, nonprogressive, congenital neuromuscular disorder. Although this entity is well known among neurologists and geneticists, the spectrum of radiologic findings in Möbius syndrome has never been illustrated. When confronted with the diverse and potentially confusing array of clinical and radiologic findings, the informed radiologist may play a significant role in suggesting the diagnosis in patients with this entity.

The original description by Möbius (1) included facial weakness and inability to abduct the eyes. In addition, a variety of congenital anomalies of the extremities and branchial musculature has been observed radiographically, including talipes equinovarus, digital anomalies, unilateral absence of pectoral musculature, congenital hip dislocation, and arthrogryposis. Unilateral absence of the pectoral musculature and digital anomalies (Poland syndrome) is a frequent association of Möbius syndrome. Swallowing difficulties leading to chronic aspiration pneumonia and emaciation are also demonstrated radiographically. The majority of these radiologic observations are illustrated in the following case report.

Case Report

An 11-year-old girl was evaluated for unusual facies and delayed development. Neurologic examination disclosed diminished gag reflex, inability to abduct the eyes, and facial diplegia manifesting as an expressionless face. Sensory function and vocal ability were normal.

During the neonatal period, the presence of flexion contractures and hypoplasia of the hands suggested a neuromuscular disorder. A delay in developmental milestones and feeding difficulties were also observed.

The child was initially brought to the hospital for correction of her malformed feet. Radiographs (Fig. 1) revealed a moderate pes cavus and metatarsus adductus. This was subsequently treated by arthrodesis.

Feeding difficulties resulting in choking and anorexia persisted. The child was frequently readmitted to the hospital for therapy of aspiration pneumonia secondary to decreased gag reflex. Chest radiographs (Fig. 2) demonstrated a persistent left-lower-lobe retrocardiac infiltrate with air bronchograms. An S-shaped thoracic scoliosis was also noted.

During evaluation of the aspiration pneumonia, a chest computerized-tomography scan (Fig. 3) revealed absence of the pectoralis major muscle on the left. This was corroborated by subsequent physical examination.

As feeding difficulties exacerbated, the child became emaciated. A barium swallow to evaluate inanition showed inability to initiate coordinated swallowing. In addition, dilatation of the first and second portions of the duodenum, with an abrupt vertical cutoff of the barium column at the third portion of the duodenum with partial obstruction (Fig. 4), was demonstrated. These ra-

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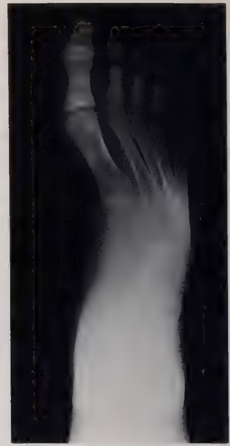


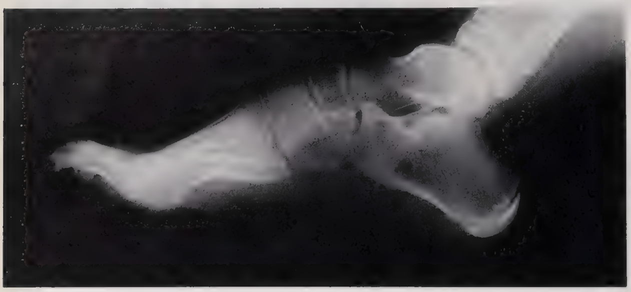


Fig. 1. Anteroposterior (**A**) and lateral (**B**) radiographs of right foot showing pes cavus and metatarsus adductus.

diologic observations are characteristic of the so-called superior mesenteric artery syndrome. A jejunostomy feeding tube was placed surgically, but the child's condition continued to deteriorate and she died following cardiac arrest several months later.

Discussion

Möbius syndrome consists of congenital cranial nerve and skeletal anomalies. In his extensive review of 45 cases, Richards (2) categorized the essential abnormalities as loss of ability to abduct the eyes, complete or partial facial weakness, and congenital anomalies affecting the extremities and branchial musculature. The hereditary pattern and etiology of Möbius syndrome remain unknown. Although the radiologic findings are consistent and significant, little attention has been given to them.

The hallmark of Möbius syndrome is congenital paralysis of the sixth and seventh cranial nerves. It is not clear, even from pathologic studies, whether the primary pathologic abnormality is absence of the respective brainstem nuclei or a disorder of facial and ocular musculature (3). Gross pathologic examination of the brain is frequently normal (4).

Since the fundamental pathologic lesion is in doubt, one may expect no characteristic brain findings on computerized tomography. However, radiologists may suggest the diagnosis of Möbius syndrome when the associated congenital abnormalities are observed in the appropriate clinical setting of a patient with facial paralysis and external ophthalmoplegia. As illustrated in the case report, these associated radiologic findings include talipes equinovarus, unilateral aplasia or hypoplasia of the pectoralis major muscle, anomalies of the hands, and swallowing difficulties complicated by emaciation and aspiration pneumonia. Congenital hip dislocation, S-shaped scoliosis, and arthrogryposis may also be demonstrated.

According to Baraitser (5), the obligatory inclusion of these primary skeletal defects in the diagnosis of Möbius syndrome excludes other disorders of muscle and anterior horn cells that present with Möbius-like facies but have a much greater hereditary predisposition. However, a study of one of the few families with multiple cases of Möbius syndrome indicates that either isolated facial weakness or isolated limb abnormalities may be a variable expression of Möbius syndrome (6).

Talipes equinovarus is present in nearly one-third of cases of Möbius syndrome (7). It is readily demonstrable radiographically and is often treated by surgical repair. Silvani et al (8) stress the consideration of Möbius syndrome in the differential diagnosis of patients with talipes equinovarus and other abnormalities.

The Poland syndrome consists of absence of the pectoralis major muscle, often associated with limb and hand anomalies. It is reported to occur

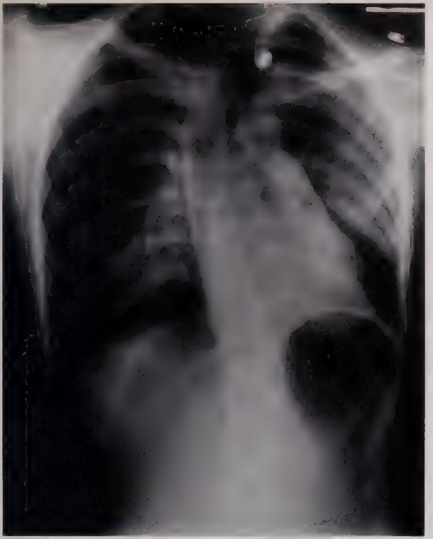
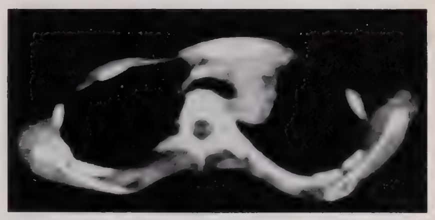


Fig. 2. Left Persistent left-lower-lobe infiltrate with air bronchograms as result of chronic aspiration. *S*-shaped thoracic scoliosis. **Fig. 3. Below** Computerized-tomography scan of chest showing asymmetry of anterior chest wall due to absence of left pectoralis major muscle.



in 13% of patients with Möbius syndrome (8). There is probably a formal genesis malformation syndrome involving both Poland and Möbius syndromes (9). In both entities, absence of the pectoralis major muscle is always unilateral.

The difficulties in swallowing are secondary to defects in cranial nerves VII, IX, and X and often result in aspiration pneumonia; prolonged tube feedings may be required (10). Fluoroscopic examination will confirm dyscoordinate swallowing. Aspiration may be noted during barium swallow or by demonstration of aspiration pneumonia on chest radiographs. As a consequence of these feeding difficulties, patients often become thin and wasted and may develop the superior mesenteric artery syndrome.

The radiologic demonstration of Möbius syndrome may thus be an aid in making the diagnosis, may determine the extent of abnormalities and complications, and may provide a framework for treatment.

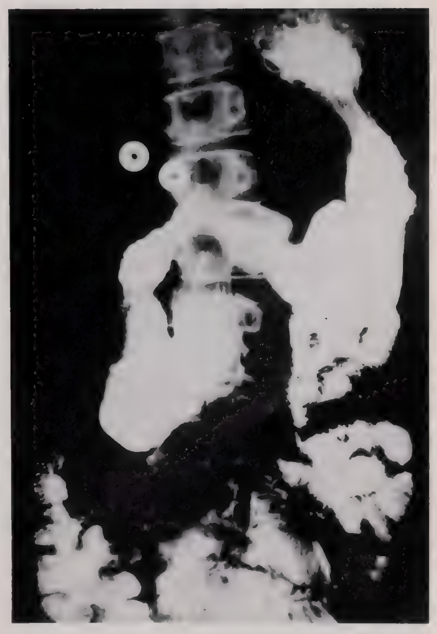


Fig. 4. Dilatation of proximal duodenum to level of partially obstructing superior mesenteric artery. Dyscoordinate swallowing was noted fluoroscopically.

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Localization of Parathyroid Adenomata By Thallium-201 and Technetium-99m Subtraction Scintigraphy

ARNOLD STRASHUN, M.D., RAFAEL A. VAQUER, M.D., AND STANLEY J. GOLDSMITH, M.D.

Abstract

Parathyroid scintigraphy was performed with serial injections and imaging of 2 mCi thallium-201 and 4 mCi technetium-99m pertechnetate in 63 patients with chemically confirmed hyperparathyroidism. Fifty-three studies were technically adequate; of these, 46 (87%) were positive (focally increased thallium uptake). Fifteen patients (15/46, 33%) underwent parathyroid exploration. Surgical correlation of 18 positive sites resulted in a positive predictive value of 72% (13/18) and a negative predictive value of 89% (8/9). Thirteen of 14 (93%) parathyroid adenomata, weighing 0.6–26 gm, were scintigraphically identified. Two false positive sites were due to thyroid adenomata. We conclude that thallium-technetium subtraction parathyroid scintigraphy is a valuable diagnostic study in the preoperative evaluation of the patient with confirmed hyperparathyroidism.

Patients with primary hyperparathyroidism are frequently detected in current practice because of routine serum calcium analysis (1, 2). Diagnosis is subsequently confirmed by measuring elevated serum parathormone (PTH) levels determined by radioimmunoassay. As a result, hyperparathyroidism is more frequently recognized at a subclinical point rather than at more advanced levels with clinical manifestations such as osteoporosis, renal calculi and dysfunction, and cerebral dysfunction (3). The disorder is treated by surgical excision (4–6).

There is a large variation in the location of the parathyroid glands, however, rendering identification and removal difficult (7, 8). A need exists, therefore, for a reliable method to identify the site of a PTH-producing adenoma prior to surgical exploration of the neck (9). Catheterization of the neck vessels with venous sampling for PTH may be definitive, but this procedure is invasive and often unsuccessful (10). Computerized x-ray tomography of the neck has not been sufficiently sensitive for this purpose (11). High-resolution ultrasound has also been unsuccessful in accurately locating smaller and/or aberrantly located parathyroid adenomata (12).

Recently, a new, noninvasive method to detect either intra- or extrathyroidal parathyroid adenomata, utilizing thallium-201 and technetium-99m pertechnetate dual-isotope subtraction scintigraphy, has been reported (13). Thallium-201 concentrates in both thyroid and parathyroid tissue by regional perfusion and ATP-dependent sodium-potassium pump function, whereas technetium-99m pertechnetate is concentrated in the thyroid alone by the iodine-trapping mechanism. A computer-stored image of pertechnetate activity in the neck may be compared and subtracted from a thallium image to identify parathyroid tissue. This report describes our initial clinical experience with a modification of this scintigraphic technique in 63 patients referred with chemical evidence of primary hyperparathyroidism.

Materials and Methods

From September 1984 to December 1985, 63 patients had been referred for parathyroid scin-

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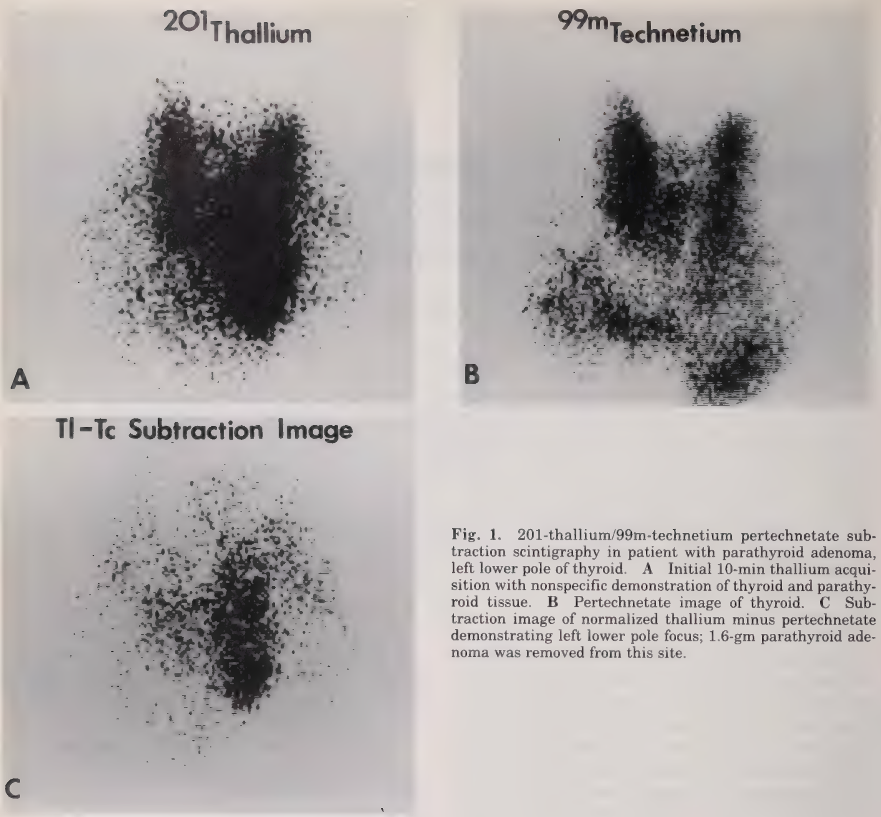

Fig. 1. 201-thallium/99m-technetium pertechnetate subtraction scintigraphy in patient with parathyroid adenoma, left lower pole of thyroid. **A** Initial 10-min thallium acquisition with nonspecific demonstration of thyroid and parathyroid tissue. **B** Pertechnetate image of thyroid. **C** Subtraction image of normalized thallium minus pertechnetate demonstrating left lower pole focus; 1.6-gm parathyroid adenoma was removed from this site.

tigraphy. All patients had chemical evidence of hyperparathyroidism documented by elevations in circulating parathormone. One patient had recurrence of hyperparathyroidism following neck exploration and partial parathyroidectomy. Careful neck palpation of all patients failed to identify palpable masses in any patients at the time of scintigraphy. All subjects gave informed consent prior to the study.

Patients were placed in the supine position with neck extended and head immobilized. A standard gamma camera (General Electric 400T or Picker 4C) with a pinhole collimator was interfaced to a digital computer (Maxdelta, CDA, Waltham, MA). For study acquisition, 2 mCi thallium-201 chloride was administered via an indwelling intravenous line, and immediate analog and digital images of the thorax were obtained for 10 min. At 10 min postinjection, the gamma camera was repositioned over the neck to include the entire anterior cervical region. Anterior thallium analog images containing 150,000 counts were obtained. A simultaneous digital image was acquired at 60 sec/frame for 20 frames in 128 × 128 word mode. At the conclusion of the thallium acquisition, 4.0 mCi technetium-99m pertechnetate was administered via the indwelling line. Two sequential anterior pertechnetate analog images of 150,000 counts were acquired, as well as digital pertechnetate images of 60 seconds per frame for 20 frames in 128 × 128 word mode.

The digitized images were processed as follows: Frames 11–20 of the thallium images were summed, as were frames 11–20 of the pertechnetate images. Summed images were individually background-corrected by standard methods. A thyroid region of interest was assigned for the background-corrected thallium and pertechnetate images, and the total counts for both were compared. The thallium image was normalized to the pertechnetate image, and the background-corrected pertechnetate image was subtracted from the background-corrected, normalized thallium image. The resultant subtraction image represents relative thallium-avid sites (Fig. 1).

Ten-minute analog imaging of mediastinal thallium distribution prior to cervical imaging was performed in the first 12 cases. Mediastinal imaging was positive in only 1 patient, who had prior negative cervical exploration for parathyroid adenomata and was therefore at higher risk of a mediastinal focus. Because of the overall low yield, mediastinal imaging was subsequently eliminated from the initial patient-imaging protocol to allow immediate cervical acquisition. Mediastinal images were taken initially only if the patient had undergone prior cervical exploration.

Results

Sixty-three studies were independently reviewed by four experienced nuclear medicine physicians. Fifty-three studies were of diagnostic quality (Fig. 2). Ten studies were not of diagnostic quality, 6 due to motion during acquisition and 4 due to poor uptake. Of the 53 diagnostic studies, 46 were positive and 7 were negative. Of the 46 positive scans, 40 studies had a single thallium focus and 6 studies had multiple foci of thallium activity. Fifteen patients with positive scans had surgical exploration. A parathyroid adenoma, weighing 0.6–26 gm, was found in 11/12 patients (92%) with a single positive focus. In one patient with a single positive focus, a thyroid adenoma was found. Of the three patients with multiple thallium foci on scintigraphy, two patients had accurate localization of a single parathyroid adenoma at one site and a coexistent thyroid adenoma at the second site. A third patient had 2 false positive sites in the lower poles of both thyroid lobes. In this patient a large (1.6 gm) parathyroid adenoma was found in the upper pole of the right thyroid lobe. This is the only unexplained false negative site identified in this group. The 3 misidentified sites (2 false positive, 1 false negative) in this patient are attributed to motion artifact.

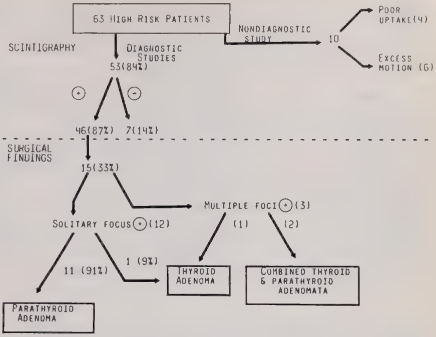

Fig. 2. Clinical-scintigraphic correlation in hyperparathyroidism.

In the 15 patients with surgical correlation of scintigraphic findings, 18 thallium avid sites were identified. Thirteen were true positive corresponding to parathyroid adenomata. One false negative site and 4 false positive sites were identified. Two of these false positive sites were found to be thyroid adenomata. The others were identified above. Overall, the aggregate sensitivity for detection of surgically confirmed parathyroid adenoma was 93% (13/14). The positive predictive value that a relative thallium-avid site was due to a parathyroid adenoma was 72% (13/18) in our experience to date.

Discussion

Since the initial description by Ferlin et al (13) of the dual-isotope subtraction method uti-

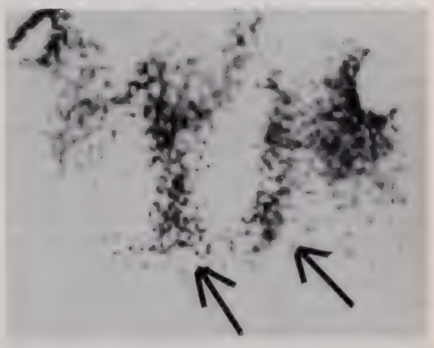

Fig. 3. Rim sign induced by motion artifact: count-normalized thallium minus pertechnetate subtraction image, demonstrating motion of patient between thallium and pertechnetate images resulting in thyroid perimeter enhancement. This finding may be confused with true parathyroid tissue.

TABLE
Parathyroid Subtraction Scintigraphy

Author	Sensitivity (TP/TP + FN)	Specificity (TN/TN + FP)	(+) Predictive value (TP/TP + FP)	(−) Predictive value (TN/TN + FN)
Ferlin (13)	18/20 (90%)	8/14 (57%)	18/24 (75%)	8/12 (67%)
Winzelberg (14)	25/31 (81%)	92/93 (99%)	25/26 (96%)	92/98 (94%)
Basarab (15)	23/25 (92%)	4/9 (44%)	23/28 (82%)	4/6 (67%)
Fogelman (16)	10/11 (91%)	8/11 (73%)	10/13 (77%)	8/9 (89%)
Ferguson (17)	10/14 (71%)	12/13 (92%)	10/11 (91%)	12/16 (75%)
McKusick (18)	12/13 (92%)	17/39 (44%)	12/36 (33%)	17/18 (94%)
Okerlund (19)	44/52 (85%)	4/16 (25%)	44/56 (79%)	4/5 (80%)
Strashun	13/14 (93%)	8/11 (73%)	13/18 (72%)	8/9 (89%)

lizing sequential technetium-99m pertechnetate and thallium-201 scintimages, several authors have reported success in noninvasively identifying parathyroid adenomata of at least 500 mg with a reported sensitivity of 71%–92% (14–19). Specificity and positive predictive value are lower, because the method identifies parathyroid and thyroid adenomata and carcinoma (Table). Thyroid adenomata were the cause of focal thallium excess in 3/15 (20%) of our surgically confirmed cases.

Our experience reveals the most frequent artifact leading to scan misinterpretation is due to inadvertent patient motion, resulting in misalignment of thallium and pertechnetate regions of distribution. This results in a typical finding in the subtraction image, an enhancement of thyroid perimeter activity (Fig. 3). This artifact may be reduced by better immobilization methods or development of computer algorithms to provide realignment of images.

In summary, our preliminary results suggest that thallium-technetium subtraction scintigraphy provides useful localizing information in patients suspected of having a parathyroid adenoma as small as 0.5 gm. Neither normal parathyroid glands nor glands less than 500 mg appear to be detectable with this method. The limited sensitivity of the method for smaller adenomata implies that a negative study in a clinical setting with convincing evidence for hyperparathyroidism should not preclude surgical exploration. Although thyroid adenoma and carcinoma are also identified by this method, this nonspecificity requires the surgeon to remain vigilant to identify a coexistent parathyroid adenoma if the original scintigraphically positive site proves negative at exploration. Nonspecific, nonparathyroid causes of a thallium-avid focus in a patient with hypercalcemia without definitive elevation of parathyroid hormone levels suggest that scintigraphy be used to localize parathyroid adenomata in the patient with clinical and chemical evidence of primary hyperparathyroidism, and not for the diagnosis of hyperparathyroidism in a nonspecific setting of hypercalcemia. Thus, in the appropriate setting of chemically confirmed hyperparathyroidism, thallium-technetium subtraction scintigraphy is justified, as localizing information simplifies the surgical management of most patients with parathyroid adenomata.

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Dysplasia in Dermatology

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Abstract

Dysplasia in dermatology may involve both specific and nonspecific cell lines. The various forms have been classified and described. Dysplasia may be either biologically benign or malignant; the term may be used to describe a variety of histologic changes, and in addition may designate—wholly or in part—a histologic diagnosis. When used in the diagnosis, it means "I don't know with absolute certainty the biologic potential of this particular lesion." Dysplastic lesions constitute important diagnostic problems in dermatopathology, and complete and adequate excision of all such lesions is recommended.

In terms of cellular biology, the histologic features of hyperplasia, anaplasia, and dysplasia can be studied with light microscopy. "Hyperplasia" indicates an increased concentration of cytologically normal cells. "Anaplasia" refers to cells that are frankly malignant. "Dysplasia" means abnormal growth, which may be cytologic, architectonic (configurational) or both. The terms "atypia" and "atypism" are also acceptable, but I prefer the term "dysplasia" because it specifically pertains to a biologic phenomenon, whereas the others do not. In dermatology, dysplasia may occur within a variety of specific cell lines, including keratinocytes, melanocytes, cells of the lymphoreticular system, cells of nerve sheath origin, and mesodermal cells of fibrohistiocytic, fatty, vascular, lymphatic, and muscular origin. In addition, I use the nonspecific descriptive terms "small," "spindle," "giant," and "pleomorphic" cell dysplasia when the specific cell line cannot be identified.

Dysplasia may be either biologically benign or malignant (Table 1); the term may be used to designate a variety of histologic changes, but also, wholly or in part, a histologic diagnosis. When used in the diagnosis, it means "I don't know with absolute certainty the biologic potential of this particular lesion." Four entities are listed in Table 1 in which the term "dysplasia" does not appear in the diagnosis because they are considered to be biologically benign by most authorities. Since, however, I believe that some of them may indeed be malignancies, they are included. I recommend complete and adequate removal of all dysplasias. I discuss briefly below the various forms within specific and nonspecific cell lines.

Keratinocytes

Three different forms of dysplasia involve the keratinocyte. One, genital keratinocytic dysplasia (1) or so-called bowenoid papulosis, is a distinct clinical and pathologic entity involving the genital skin and mucosa of young adults, all showing histologic features indistinguishable from squamous-cell carcinoma in situ. This entity encompasses a spectrum of different disorders, including bona fide in-situ carcinoma (Bowen's disease), benign, possibly viral-induced atypia, and in-situ carcinoma or benign atypia induced by viruses and/or podophyllin (long-term effect) or other local irritative agents or factors acting on preexisting lesions such as warts, seborrheic keratoses, or skin tags.

Another form of dysplasia, sclerosing keratinocytic lesion (2), is considered by some to represent a distinct benign clinical and pathologic entity termed desmoplastic trichoepithelioma (3) and sclerosing epithelial hamartoma (4). Clini-

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TABLE 1
Dysplasia

Specific cell line
Keratinocyte
  Genital keratinocytic dysplasia
  Sclerosing keratinocytic lesion
  Basal cell proliferation with dysplasia
    1. and features of a trichoepithelioma
    2. overlying a dermatofibroma
    3. and sebaceous differentiation
    4. and features of a pilomatricoma
Melanocyte
  Spindle and epithelioid cell nevus
  Melanocytic nevus with dysplasia (dysplastic nevus)
  Melanocytic dysplasia
Lymphoreticular cells
  Cutaneous atypical regressive reticulosis (lymphomatoid papulosis)
  Lymphoid dysplasia
Nerve sheath cells
  Nerve sheath neoplasm with dysplasia
Muscle cells
  Leiomyomatous proliferation with dysplasia
Fibrohistiocytic cells
  Atypical fibroxanthoma
  Dermatofibroma (histiocytoma) with dysplasia
Fat cells
  Lipomatous proliferation with dysplasia
Vascular and lymphatic cells
  Angiomatous proliferation with dysplasia
Nonspecific cell line
Small-cell proliferation with dysplasia
Spindle-cell proliferation with dysplasia
Giant-cell proliferation with dysplasia
Pleomorphic-cell proliferation with dysplasia

cally, they are described as annular, indurated lesions with a raised border and nonulcerated depressed center, generally involving the face. Histologically, these lesions showed a constant triad of narrow strands of basaloid tumor cells, keratinous cysts, and desmoplastic stroma. I believe, however, that some, if not many, of the cases reported as such are sclerosing basal cell carcinomas. In my experience, the sclerosing basal cell carcinomas and these reported cases may be clinically and histologically indistinguishable. Thus, although some of these cases may be benign sclerosing keratinocytic lesions of pilosebaceous origin, perhaps sclerosing variants of a trichoepithelioma, the histologic changes do not permit distinctions and, hence, do not indicate their biologic potential.

Probably the most infrequently encountered form of keratinocytic dysplasia is the least notorious. I term this "basal cell proliferation with dysplasia." It has no characteristic clinical picture, and the diagnosis is based purely on histopathology. Four distinct histologic patterns may be observed:

- Lobular proliferation of relatively uniform basophilic epithelial cells resembling basal cells showing peripheral palisading, little or no mitotic activity, stromal retraction artifact, keratinization or horn cysts, no evidence of hair papilla formation, and a variable but generally loose stromal proliferation. The differential diagnosis rests between a trichoepithelioma and a basal cell carcinoma.
- Multiple buds, nests, and cords of basophilic epithelial cells resembling basal cells connected to the basal layer of a hyperplastic epidermis at multiple sites with apparent extension into the subjacent papillary cutis associated with peripheral palisading, occasional mitoses, and stromal retraction artifact overlying a dermatofibroma. The differential diagnosis rests between basal cell hyperplasia and a creeping basal cell carcinoma.
- Lobular proliferation of basophilic epithelial cells resembling basal cells showing peripheral palisading, little or no mitotic activity or stromal retraction artifact, an obvious but variable degree of differentiation toward mature-appearing sebaceous cells (minimal or absent in some lobular proliferations), occasional keratin-containing ductular structures, and foci of squamous differentiation. The differential diagnosis rests between a sebaceous adenoma and a basal cell carcinoma with sebaceous differentiation.
- Poorly circumscribed lesion composed of a preponderance of sheets of basophilic epithelial cells resembling basal cells that show peripheral palisading, frequent mitotic activity, and zones of necrosis that merge with relatively small sheets of shadow cells surrounded by a stroma showing fibrosis and a foreign-body reaction. The differential diagnosis rests between a pilomatricoma and the rare malignant pilomatricoma (a basal cell carcinoma of hair germ origin).

Melanocytes

The spindle and epithelioid cell nevus is considered by virtually all authorities to be unequivocally biologically benign, although histologic dysplasia of variable degrees is a characteristic feature of perhaps the majority of lesions. Even in the face of severe histologic dysplasia, these lesions are diagnosed as such when they are observed in children, as are most cases. I believe that to be a fallacy. Some cases so diagnosed may be malignant melanomas; instances have been reported (5). It should not be forgotten that malignant melanomas do not occur in children.

"Melanocytic dysplasia" refers to a variety of histologic changes (Table 2) and is also a histologic diagnosis. This dysplasia may occur alone or in combination with a clearly benign melanocytic component, such as the lesion termed "dysplastic nevus." It may be confined solely to the epidermis or epithelium, the dermis or lamina propria, or may involve both sites. Except for the infrequent melanocytes within endothelial-lined channels, a pathognomonic feature of malignancy in malignant melanomas, the histologic features of melanocytic dysplasia also represent the criteria for the diagnosis of malignant melanoma. Although there are published reports (6) of angioinvasion by melanocytes within benign melanocytic lesions, I find them unconvincing. Some cases may be apparent and represent stromal retraction artifact. Some cases may be apparent and represent stromal retraction artifact. Other cases that clearly demonstrate the presence of melanocytes within endothelial-lined channels cannot be interpreted as invasion in a totally benign lesion showing no other histologic criteria of dysplasia. This also must represent artifact, possibly induced during sectioning.

In the absence of lymphatic or blood vessel invasion, the histologic diagnosis and, hence, differences between melanocytic dysplasia and malignant melanoma are dependent on the sum total, frequency, and degree of dysplastic changes. A comparative histologic analysis reveals a number of differences, many of them subtle, that help to distinguish them (Table 3).

Unfortunately, lesions showing the histologic features of melanocytic dysplasia have been incorrectly designated by others as "active" or "activated" nevi (7), "atypical melanocytic hyperplasia" (8), and "borderline" (9) malignant melanoma or lesion. In fact, some authors designate bona fide in-situ malignant melanomas as "atypical melanocytic hyperplasia" and "precancerous melanosis." Because one is dealing with dead tissue, and the presence of dysplastic melanocytes may or may not signify that the lesion was actively growing in vivo, the term "active" or "activated" is inappropriate. Melanocytic hyperplasia implies increased concentration of normal melanocytes and is never "atypical." Therefore, the term "melanocytic hyperplasia" should never be used for in-situ malignant melanomas. By the same token, the latter are bona fide in-situ cancers and should never be termed "precancerous." Once atypism occurs, melanocytic dysplasia is present. Although the biologic potential of a lesion may be equivocal and uncertain in the pathologist's mind, a lesion has already been programmed to be either histologically benign or malignant. A "borderline" malignant melanoma is therefore nonexistent.

TABLE 2

Histologic Features of Melanocytic Dysplasia

Cytologic

Nuclear hyperchromatism and variation in size and shape
Large nucleoli
Mitoses
Variations in cell size and shape
Abundant relatively clear cytoplasm laden with dustlike melanin granules

Architectonic

Continuous band of cytologically dysplastic melanocytes at dermal-epidermal (lamina propria–epithelial) junction and/or extension of this band well beyond dermal or lamina propria component of a melanocytic lesion
Junctional nests of melanocytes (with or without cytologic dysplasia) well beyond dermal or lamina propria component of a melanocytic lesion
Melanocytes (with or without cytologic dysplasia) occurring singly or in nests at various levels of epidermis or epithelium
Large nests of melanocytes (with or without cytologic dysplasia) at any level
Melanization at depths of a melanocytic lesion
Evidence of regression within subepidermal or subepithelial zone of a melanocytic lesion
Absence of maturation with depth of a melanocytic lesion
Inflammatory cell infiltrate intimately associated with dermal or lamina propria component of a melanocytic lesion
Lymphatic and/or blood vessel invasion

Lymphoreticular Cells

I recognize two forms of lymphoreticular cells. One I term "cutaneous atypical regressive reticulosis" (10), or so-called lymphomatoid papulosis. This is a dinstict clinical and pathologic entity, in the medical literature for approximately twenty years, having the clinical picture of Mucha-Habermann disease and the histologic features of a malignant lymphoma in which the dysplastic lymphoid cells comprising the infiltrate are T lymphocytes. The dysplasia is both architectonic and cytologic, the latter often severe. Although a majority of cases regress spontaneously, a significant number progress to a systemic malignant lymphoma.

I believe this entity may represent either of two possibilities, clinically and histologically indistinguishable: either a primary cutaneous T-cell malignant lymphoma (mycosis fungoides) unrelated to Mucha-Habermann disease, but showing a high rate of spontaneous regression, or Mucha-Habermann disease. If the latter, then it could be either a benign histologic variant with occasional conversion to malignant lymphoma, or simply one of a spectrum of histologic manifesta-

TABLE 3
Histologic Differences between Melanocytic Dysplasia and Malignant Melanoma

Feature	Melanocytic dysplasia	Malignant melanoma
Nucleus	Usually single, occasionally binucleated	Frequently binucleated and multinucleated
Mitoses	Infrequent, often absent	Sparse to abundant, rarely absent
Intranuclear eosinophilic bodies	Never within epidermis or epithelium; rare within dermis or lamina propria	Often at any level
Location	Usually basal and lower half of malpighian layers and papillary cutis or superficial lamina propria (with or without nevus cells), but may involve all levels	Usually basal and lower half of malpighian layers and all levels of cutis or lamina propria; often involve all levels of epidermis or epithelium
Growth pattern	Single cells, linear bands, or associated with nevus cell nests within epidermis or epithelium, often extending well beyond dermal or lamina propria component of a melanocytic nevus and usually associated with solitary and contiguous nevus cell nests in dermis or lamina propria	Single cells and solitary and contiguous nests in epidermis or epithelium and solitary and contiguous nests and cords in dermis or lamina propria
Nesting	Only when associated with nevus cells, occasionally large	Usually present, often inconspicuous, may be absent in lentigo maligna
Single melanocytes at all levels of epidermis or epithelium	Rarely present	Often present
Adjacent inflammation	Usually absent	Generally present
Lymphatic and/or blood vessel invasion	Never	Infrequent

tions of a primary cutaneous T-call malignant lymphoma, if one accepts the premise that Mucha-Habermann disease is a primary cutaneous T-cell malignant melanoma in all of its histologic manifestations. Because this entity may represent a bona fide malignant lymphoma, and many lesions are nodules as well as papules, the term "lymphomatoid papulosis" is a misnomer. Cutaneous atypical regressive reticulosis accurately describes this entity. All patients with this diagnosis or the diagnosis of Mucha-Habermann disease should have frequent checkups and multiple biopsies to detect and treat early progression to malignant systemic disease.

A diagnosis of lymphoid dysplasia encompasses all cases with dysplastic lymphoid infiltrates. The dysplasia may be either architectonic and cytologic or purely architectonic. Without cytologic dysplasia, the dysplastic features include: large, compact aggregates of mature-appearing lymphoid cells; the presence of these cells at all levels of the cutis, often abutting and attenuating the epidermis, and within the subcutaneous tissue; infiltrates of these cells between collagen bundles and fat cells; and individual cells or aggregates of these cells at various levels of the epidermis.

The biologic potential of these lesions can only be determined with certainty retrospectively. Benign lesions include lymphocytoma cutis, lymphocytic infiltration of the skin of Jessner, arthropod bites, some drug eruptions, a polymorphous light eruption of the plaque type, actinic reticuloid, and lupus erythematosus. Aggressive lesions include the various leukemias and malignant lymphomas, especially the well-differentiated lymphocytic forms.

Nerve Sheath Cells

Dysplasias within nerve sheath cells are uncommon. They include all spindle-cell neoplasms clearly composed primarily of cells of nerve sheath origin, that is, Schwann cells. These lesions often show severe cytologic dysplasia, with large cells having large, bizarre hyperchromatic nuclei, frequently multinucleated. Architectonic dysplasia may be absent. When present, it is not striking and generally consists of poorly circumscribed, compact cellular fascicles of spindled cells, which at times seem to invade adjacent tissue.

The differential diagnosis rests between a neurofibroma or neurilemmoma showing severe degenerative changes and a nerve sheath sarcoma.

Muscle Cells

With the exception that lesions in muscle cells are clearly composed wholly of cells of smooth muscle origin, what has been said of nerve sheath dysplasia also holds for this dysplasia. In this case, however, the differential diagnosis rests between a leiomyoma showing degenerative changes and a leiomyosarcoma.

Fibrohistiocytic Cells

Two different forms of dysplasia are encountered in fibrohistiocytic cells. One of them, atypical fibroxanthoma, is a relatively rare, distinct clinicopathologic entity. Generally, it is characterized clinically by a rapidly growing papule or nodule on sun-damaged skin in an elderly individual. Histologically, although all levels of the skin, including the subcutaneous tissue, may be involved, it tends to be located primarily within the papillary cutis, often with overlying ulceration. Cytologic dysplasia is severe. Spindled cells predominate but multinucleated giant cells are often numerous. Mitoses are usually abundant. Architectonic dysplasia, as described for nerve sheath and muscle cell dysplasia, may be absent or limited to poorly circumscribed, compact cellular aggregates of spindle cells that appear to invade adjacent tissue.

Most authorities consider this lesion to be a benign, reactive proliferation, possibly to trauma. Retrospectively, however, many cases have proven to be malignancies with manifestations of metastatic disease (11), representing an undifferentiated sarcoma, perhaps a variant of a malignant fibrous histiocytoma. Thus, this is indeed a dysplasia. Although reported, I doubt the existence of such lesions on skin that is not sun-damaged.

The dermatofibroma (histiocytoma) with dysplasia is a relatively common lesion with a wide range of histologic patterns. Architectonic dysplasia is similar to that of the atypical fibroxanthoma and the nerve sheath and muscle cell dysplasias. Cytologic dysplasias may range from mild to severe.

The differential diagnosis rests between a benign cellular dermatofibroma (histiocytoma) and aggressive lesions such as a dermatofibroma protuberans and a malignant fibrous histiocytoma.

Other Cells

Fat Cells. Dysplasias in fat cells are extremely rare. Architectonic dysplasia may be absent or mild, and cytologic dysplasia may range from mild to severe. The differential diagnosis rests between a lipoma with degenerative changes and a differential liposarcoma.

Vascular and Lymphatic Cells. In vascular and lymphatic cells one encounters angiomatous lesions with varying degrees of cytologic endothelial dysplasia. Architectonic dysplasia may be absent or characterized by compact, poorly circumscribed aggregates of endothelial-lined channels with apparent invasion of adjacent tissue. The differential diagnosis rests between a benign hemangioma or lymphangioma and an angiosarcoma.

Nonspecific Cell Line. In the nonspecific cell line are dysplastic lesions of extremely varied and undifferentiated cell types in which the cell line of origin cannot be determined. As one would expect, cytologic and architectonic dysplasia vary considerably, and the differential diagnosis rests between a multitude of both benign and malignant lesions.

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Primary Cryptococcal Pneumonia Mimicking *Pneumocystis carinii* Pneumonia in a Patient with AIDS

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Abstract

The most common pulmonary complication of AIDS is *Pneumocystis carinii* pneumonia (PCP). However, other opportunistic infections also may present with diffuse pulmonary involvement. Cytomegalovirus pneumonia and *Mycobacterium avium intracellulare* infection have been reported to mimic PCP. We report a patient with disseminated cryptococcosis whose initial diffuse pulmonary involvement and radiographic findings were indistinguishable from PCP. The diagnosis of cryptococcosis was suggested by the presence of yeastlike budding cells with concentric halos and the demonstration of high titers of cryptococcal antigen in the bronchial washings. *Cryptococcus neoformans* must be added to the list of organisms that can produce rapidly progressive interstitial pneumonia in a patient with AIDS and, thereby, increases the urgency to establish a microbiologic diagnosis in this clinical setting, especially since cryptococcal infection is potentially treatable with antifungal agents. We demonstrate that rapid identification of pulmonary cryptococcal infection is possible through microscopy and determination of cryptococcal antigen in bronchial washings.

Pneumocystis carinii pneumonia (PCP) is the most frequent life-threatening opportunistic infection occurring in patients with the acquired immunodeficiency syndrome (AIDS). We describe a patient whose initial clinical symptoms and radiographic evidence were highly suggestive of and initially confused with PCP, but which were caused by *Cryptococcus neoformans*. *C. neoformans* infection may mimic PCP and other more common diffuse pneumonias in patients with AIDS. Rapid diagnosis is essential and is readily achieved by demonstrations of the fungus and high titers of cryptococcal antigen in bronchial aspirates.

Case Report

A 30-year-old heterosexual man, an intravenous drug abuser for fifteen years, developed anorexia, weight loss, and fatigue one month prior to admission. Two weeks later he noted drenching night sweats, temperatures to 103° F, and chills. He was treated with oral erythromycin without improvement. One week prior to admission he began experiencing dyspnea on exertion. He reported no cough, dysuria, or hematuria. He did report a 20-lb weight loss. His medical history was significant for hepatitis of unknown type several years earlier and "anemia." His medications included methadone, 70 mg/day, and thorazine. The patient was married, without children, and worked as a truck driver. He drank alcohol socially and smoked marijuana, but not cigarettes. For the past 15 years he was in a methadone maintenance treatment program but continued to use intravenous heroin and cocaine. He was born in Cuba and came to the United States at age 12.

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Physical examination revealed a well-developed white man, lethargic but easily arousable, and oriented to person, place, and time. He had received his methadone 20 min prior to arriving in the emergency room, where he was found to have a blood pressure of 110/60 mm Hg, temperature of 101° F, and respiratory rate greater than 30/min. He had constricted but reactive pupils, and the disc margins were sharp. Oral candidiasis was present. His neck was supple and there was no jugular venous distention. He had shotty posterior cervical axillary lymph nodes. Lung examination revealed normal breath sounds, without wheezes or rales. Cardiac examination was normal. His abdomen was soft, with mild right-upper-quadrant tenderness. The liver was enlarged and the spleen tip was palpable. There was no costovertebral angle tenderness. Rectal examination revealed external hemorrhoids; there was no occult blood. The extremities were remarkable for the presence of needle marks on both arms. Meningeal signs were absent.

Laboratory data revealed a white blood cell count of 7,500/mm^3 with 88% polymorphonuclear leukocytes, 1% bands, 8% lymphocytes, 1% eosinophils, and 2% monocytes. Hemoglobin was 14 gm/dL, hematocrit 41%, and mean corpuscular volume 75/mm^3. Platelet count was normal. Prothrombin time was 13.1 sec/11.7 sec, erythrocyte sedimentation rate 6 mm/hr (Westergren). Urinanalysis was normal. Blood chemistries, including liver function tests, were normal except for an albumin of 2.8 gm%. Arterial blood gas taken with the patient breathing room air was PaO_2 62 Torr, $PaCO_2$ 34 Torr, and pH 7.47. Electrocardiogram showed a sinus tachycardia. Chest x-ray was normal (Fig. 1).

The patient was admitted with the diagnosis of probable AIDS, and treatment with intravenous trimethoprim-sulfamethoxasole for presumed PCP was initiated. The following day he underwent fiberoptic bronchoscopy with a transbronchial biopsy of the right lower lobe. The patient bled approximately 100 cc after the biopsy. No formal bronchoalveolar lavage was performed.

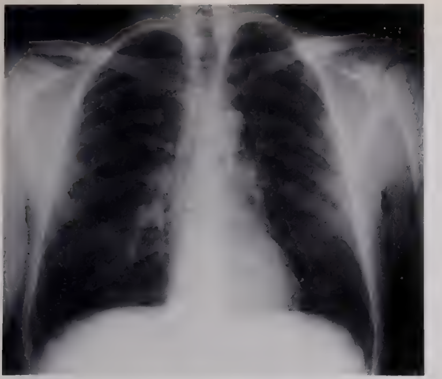
Microbiologic Findings. In addition to tissue sent in formalin for pathologic analysis, a single slide was prepared from bronchial secretions and forwarded to the microbiology laboratory. Because *P. carinii* infection was strongly suspected, the slide was Giemsa-stained and evaluated. In the first microbiologic field a large mononuclear cell was observed with numerous round oval bodies within the cytoplasm (Fig. 2). These oval bodies were pale lavender and encircled by a faint halo. Continued review of the slide showed numerous other macrophages containing from 3 to 28 oval bodies. Because of their intracellular location, tinctorial staining quality, and microscopic morphology, the ovoid cells bore a striking resemblance to *Histoplasma capsulatum*. In addition, there was an unusual extracellular presence of poorly stained, large, oval, yeastlike cells with a well-circumscribed concentric halo. In other fields similar budding cells were observed in which the halo conformed to the contour of the budding cell. These latter morphologic aspects were highly suggestive of *Cryptococcus*.

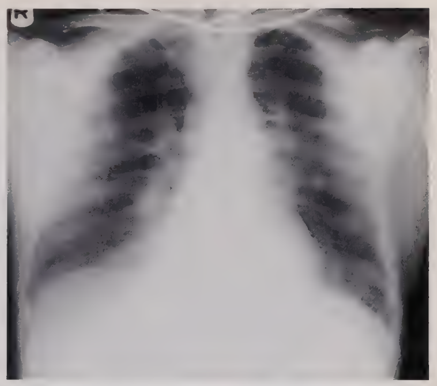
In the absence of additional slides for differential staining, and in order to resolve the diagnostic problem, the bronchial washings were assessed for cryptococcal antigen. This was achieved by emulsifying some of the highly bloody washings in sterile distilled water and passing the solution through a 0.45 filter. The clear filtrate was then interacted with latex particles coated with cryptococcal anticapsular antibdy. This resulted in a strong agglutination to a titer of 1:256. At this point a diagnosis of cryptococcal pneumonia, with a remote possibility of concurrent histoplasmosis, was made.

Following these events the patient underwent a lumbar puncture. The cerebrospinal fluid (CSF) glucose was 75 mg%, and the total protein was 24 mg%. The fluid content of red blood cells was 24/mm^3 and of white blood cells, 2/mm^3. Of 16 white blood cells counted, there were 14 lymphocytes, 1 monocyte, and 1 polymorphonuclear leukocyte. India ink preparation of the CSF showed numerous encapsulated yeast cells, both single and budding. The CSF cryptococcal antigen titer was 1:8192.

The bronchial secretions and CSF were cultured in a variety of media designed to support the growth of mycotic agents. Included were Sabouraud's dextrose agar with and without antibiotic supplementation and cycloheximide, Sabhi's brain heart infusion agar with 5% human blood, and Dubos liquid media. The latter media were held for one month. The cultures were positive only for *C. neoformans*. In addition, the results of the transbronchial biopsy later confirmed the diagnosis of cryptococcal pneumonia.

Upon recognition of *Cryptococcus* as the infecting organism in this patient, treatment was changed to amphotericin B. Postbronchoscopy chest x-ray (Fig. 3) revealed a diffuse interstitial pneumonia. Chest examination demonstrated





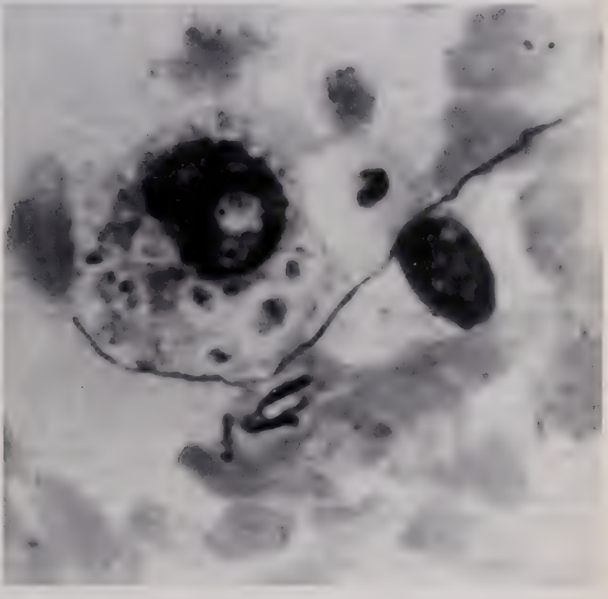


Fig. 1. Upper Left Normal chest x-ray on admission. **Fig. 2. Right** Bronchial secretion showing macrophage with numerous round to oval intracytoplasmic bodies (Giemsa stain, original magnification ×100). **Fig. 3. Upper right** Despite differences in technique, this chest x-ray taken on the second day reveals diffuse interstitial pneumonia.

scattered rales. Later that evening the patient became increasingly dyspneic and hypoxemic. His respiratory rate was 36, and the arterial blood gas with the patient breathing 50% oxygen showed PaO_2 50 Torr, $PaCO_2$ 27 Torr, and pH 7.47. Meningeal signs remained absent. The patient's respiratory status rapidly worsened. He developed a supraventricular tachycardia of 180/min which responded to 5 mg of intravenous verapamil. Shortly after endotracheal intubation the patient developed bradycardia and hypotension. His PaO_2 was less than 40 Torr during manual bag ventilation on 100% oxygen. Cardiac arrest ensued and despite vigorous attempts at resuscitation, the patient died.

Pathologic Findings. At autopsy, needle marks were found in the antecubital fossae bilaterally. Pulmonary hemorrhage and an associated thromboembolus were found in the right lower lobe. Organomegaly was prominent. The lungs weighed three times, the liver and kidneys twice, and the spleen six times the expected weight. There was no permission to examine the brain. Disseminated cryptococcal infection involving the lungs, liver, kidneys, adrenals, thyroid, heart, spleen, lymph nodes, and spinal cord meninges was found. Encapsulated organisms ranging in size from 10 to 25 μm (mean 15 μm) were found in these affected organs. In the lungs, the organisms were predominantly interstitial (Fig. 4). At every site the surrounding inflammation was minimal and, where present, was predominantly mononuclear. Mucin and PAS stains delineated cells with varying degrees of encapsulation. No other organisms or viral inclusions were seen. *P. carinii* was not present and there was no evidence of Kaposi's sarcoma. A peculiar finding was noted in the hemorrhagic areas of the lungs. Here, a cryptococcal capsule appeared to be incorporating some blood component, for it stained intensely red on routine hematoxylin-and-eosin staining (Fig. 5). This phenomenon has, to our knowledge, not been described before.

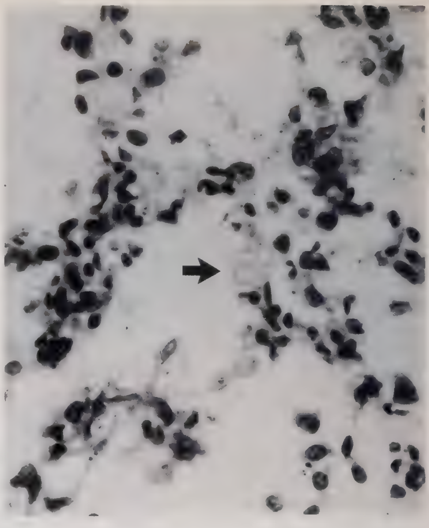


Fig. 4. Encapsulated organism (arrow) in interstitium of lung (hematoxylin and eosin, original magnification ×40).

Discussion

C. neoformans is a ubiquitous, encapsulated, unimorphic fungus that exists in yeast form (1–4). Its portal of entry into humans is via the respiratory tract, but only rarely does it cause clinically apparent pulmonary disease (1, 3, 5). As many as 50% or more of patients with cryptococcal disease have compromised cell-mediated immune responses (1, 3, 6). Patients at risk of developing cryptococcosis are those being treated with corticosteroids or immunosuppressive agents, as well as those with AIDS, reticuloendothelial malignancies, systemic lupus erythematosis, sarcoidosis, and chronic lung disease (1–3, 6, 7). Cryptococcal infection may remain localized to the lungs or may disseminate hematogenously to other organs. *C. neoformans* has a particular predilection for the central nervous system, where it causes meningitis (1, 3, 8). The immunocompromised host is more likely to develop disseminated disease (3). In a report of renal transplant patients with cryptococcal infection, 9 of 10 had central nervous system involvement, 8 with meningitis and 1 with a brain granuloma (2).

Although the respiratory tract is the most common site of infection, pulmonary cryptococcosis is often not diagnosed because it is frequently asymptomatic and self-limited (1, 3, 4, 8). Symptoms, when present, consist of a nonproductive cough, low-grade fever, and/or slight weight loss (3–5, 8). The chest x-ray may be normal or may demonstrate a well-circumscribed mass 2–10 cm in diameter that is often confused with a bronchogenic carcinoma (3). Segmental or lobar consolidation is another possible finding on chest x-ray (3). In disseminated disease, the chest x-ray may show multiple indistinct nodules, peribronchial infiltrates, or—rarely—a diffuse miliary pattern (3, 5, 6, 8).

Treatment for cryptococcosis with amphotericin B alone or in combination with flucytosine should be administered when there is disseminated disease, worsening of pulmonary symptoms, the presence of underlying disease, or the administration of corticosteroids (5).

In recent years *C. neoformans* has become an important pathogen in patients with AIDS. *Cryptococcus* is the fourth most commonly recognized organism causing life-threatening infection, following cytomegalovirus (CMV), *P. carinii*, and *Mycobacterium avium intracelluare* (MAI), in patients with AIDS followed at the National Institutes of Health (7). As in other immunocompromised hosts, patients with AIDS and cryptococcal infection most commonly have symptoms of central nervous system involvement. In a recent re-

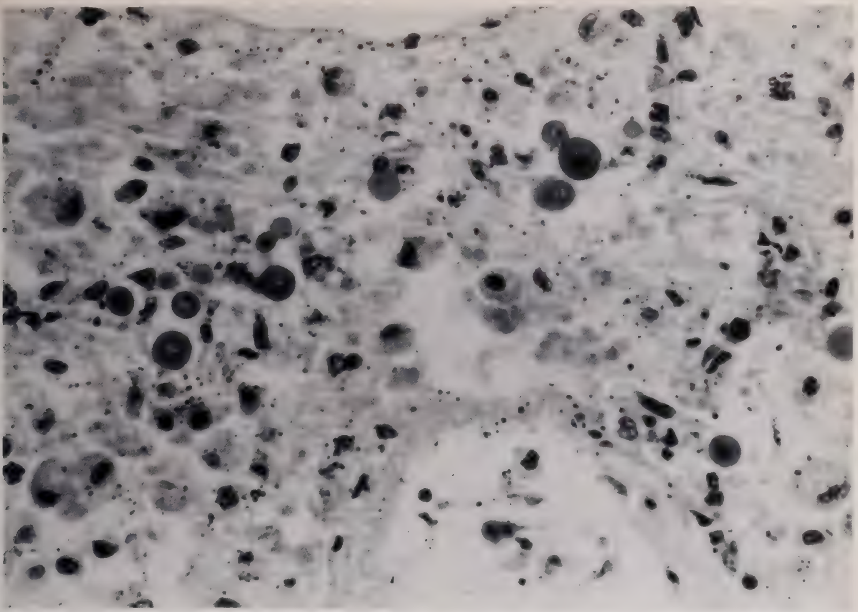


Fig. 5. Alveolar hemorrhage; encapsulated organisms with intensely red-staining capsule and minimal surrounding inflammation (hematoxylin and eosin, original magnification, ×40).

view of cryptococcosis in AIDS patients, only 1 of 27 patients had pulmonary symptoms as the initial manifestation of cryptococcal disease. This patient had a right middle lobe lobar pneumonia. Eighteen of 27 patients initially had meningitis and encephalitis (7).

At The Mount Sinai Medical Center, New York, between December 1981 and December 1983, 64 patients at high risk of developing AIDS underwent bronchoscopy because of persistent cough, dyspnea, or abnormal chest x-ray. Forty-eight of these patients were found to have opportunistic infections, Kaposi's sarcoma, or lymphoproliferative disorders. Bronchoscopic findings revealed 32 of these 48 patients (67%) to have PCP, 5 (10%) CMV pneumonia, and 2 (4%) nontuberculous mycobacterial infections. The remaining patients were infected with a variety of other organisms, including *Hemophilus influenzae, Staphylococcus aureus,* and *Histoplasma capsulatum.* There were no cases of cryptococcal infection (9). The special report from the National Heart, Lung, and Blood Institute on the pulmonary complications of AIDS reported that of 441 patients with AIDS and pulmonary disease, 373 (85%) had PCP. Of these patients with PCP, 118 (32%) had coexisting infections with other organisms, 8 (7%) with *C. neoformans* (10).

P. carinii, CMV, and MAI are known to produce diffuse interstitial pneumonias in patients with AIDS. These patients often initially have progressive dyspnea and/or cough. In this report we describe a patient with disseminated cryptococcosis whose initial pulmonary symptoms and radiographic findings were indistinguishable from the more common PCP. *C. neoformans* must be added to the list of organisms that can cause diffuse interstitial pneumonia in patients with AIDS (11). Since cryptococcal infection is potentially treatable with antifungal agents, an early microbiologic diagnosis is essential. Cryptococcal antigen is detectable in the sera and cerebrospinal fluids of patients with cryptococcal infection (7, 12). We have demonstrated that rapid identification of cryptococcal antigen in bronchial secretions is possible and will give strong support to the diagnosis of pulmonary infection with *C. neoformans.*

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Fatal Pulmonary Lipid Embolism Associated with Taxol Therapy

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Pulmonary lipid embolism is a well-known complication of long-bone fractures and may also occur in association with soft-tissue injury, extensive cutaneous burns, fatty liver (1), and steroid administration (2, 3). It has also been reported rarely as a complication of infusion of lipid emulsions in neonates (4) and adults (5). We report a case of fatal pulmonary lipid embolism that occurred during administration of Taxol (BenVenue Laboratories, Bedford, OH; supplied by the National Cancer Institute, Bethesda, MD), an investigational water-insoluble chemotherapeutic agent that is formulated in the oil-based vehicle Cremophor EL (Bass Wyandotte, Parsippany, NJ).

Case Report. A 51-year-old white woman underwent right upper and middle lobectomy for adenocarcinoma of the lung in 1982 and right lower lobectomy for tumor recurrence in 1984. Two months later, metastases developed in the left lung. She was treated unsuccessfully with a variety of chemotherapeutic regimens, including cyclophosphamide, doxorubicin, cisplatin, 5-fluorouracil, mitomycin-C, ectoposide, methotrexate, and lomustine. A series of chest x-rays during the treatments showed progressive enlargement of preexisting nodules and development of new ones. Although she was still ambulatory, her activities were severely limited by exertional dyspnea. She was admitted to this hospital for a chemotherapeutic trial with Taxol. Medications at the time of admission included prednisone, 10–20 mg daily.

On physical examination her blood pressure was 100/70 mmHg, pulse rate 120/min, and respirations 28/min. Breath sounds were normal on the left side and absent on the right. There were no adventitious cardiac sounds. The extremities were free of clubbing and edema. Chest x-ray revealed an opacified right hemithorax and diffuse nodular disease in the left lung. Hematologic parameters were normal except for a leukocyte count of 15,000/μl with normal differential. No significant abnormalities were seen in serum chemistry analytes, including lipids.

Taxol was infused over 24 hours through an in-line filter (Ivex HP Filterset-SL) at a dose of 250 mg/m^2, for a total of 368 mg in 4 liters D$_5$W. The fluid concentration of Taxol was 0.092 mg per milliliter of Cremophor (0.765% by volume). Based on stability tests, the National Cancer Institute recommends the following rates of administration of Taxol: 0.6 mg/ml in 5% D$_5$W or normal saline, administered within 4 hours; 0.36 mg/ml in D$_5$W within 6 hours; and 0.009 mg/ml in D$_5$W within 24 hours. Furosemide was administered concurrently, and adequate urine output was maintained throughout the infusion.

Twelve hours after the start of the infusion the patient complained of chest pain. Respirations were 40/min, blood pressure 120/80 mmHg, pulse 128/min, and temperature 39°C. Chest x-ray revealed diffuse haziness of the left lung; however, the dypsnea improved after an additional bolus of furosemide. Twelve hours later the dyspnea recurred. The patient was placed on 4

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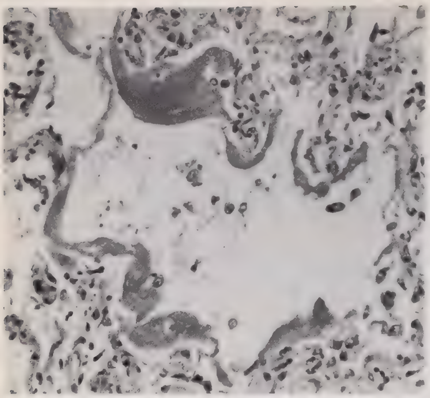

Fig. 1. Diffuse alveolar damage with hyaline membrane deposition (hematoxylin and eosin, 40 × original magnification).

liters/min O_2 by nasal cannula and arterial blood gas tests showed pH 7.52, pCO_2 26 mmHg, and pO_2 64 mmHg. Despite treatment with furosemide and morphine, the patient's respiratory status deteriorated further, and she required intubation and mechanical ventilation. With the patient on 100% O_2, a subsequent arterial blood gas revealed pH 7.42, pCO_2 33 mmHg, and pO_2 45 mmHg. She became hypotensive and died 36 hours after the onset of symptoms.

At autopsy, the left lung weighed 1000 g and was extensively infiltrated by adenocarcinoma. Tumor was present at the carinal stump and in the right diaphragm, periaortic lymph nodes, transverse colon mesentery, bone marrow, kidney, and adrenal gland. The areas of lung uninvolved by tumor revealed diffuse alveolar damage with hyaline membrane deposition (Fig. 1) as well as numerous dilated, empty-looking capillaries and arterioles. There was no evidence of pulmonary edema or thromboembolism. Osmic acid stains on fresh and formalin-fixed tissue demonstrated multiple lipid emboli within pulmonary arterioles, capillaries, and alveolar spaces (Fig. 2). No hematopoietic elements were seen accompanying the lipid emboli. A few scattered lipid emboli were also present within arterioles of the heart and kidneys. There was no evidence of myocardial infarction or coronary artery occlusion. There were no apparent bone fractures resulting from terminal resuscitative efforts. The brain was not included in the autopsy.

Discussion. Taxol [tax-11-en-9-one,5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxy-4,10-diacetate 2-benzoate 13-(α-phenylhippurate)], an alkaloid derived from the Pacific Western yew *Taxus brevifolia,* is an investigational chemotherapeutic agent that is supplied in Cremophor EL/ethanol. Its tumoricidal activity is attributed to its ability to induce irreversible aggregation of microtubules (6). Cremophor is a nonionic emulsifying agent consisting of castor oil (ricinoleic acid) and ethylene glycol. It is most commonly used as a vehicle for such water-insoluble drugs as cyclosporine, teniposide, and echinomycin; the usual doses with these drugs are 4–5 ml, 15 ml, and 4–5 ml, respectively. Our patient received 30.7 ml of Cremophor in a 24-hour period. Other patients at this hospital have received more than 40 ml of Cremophor in the same period without this complication.

The major side effects of Taxol in animals are myelosuppression and gastrointestinal toxicity (7). In phase I clinical trials, the main dose-limiting toxicity is myelosuppression. Other toxic symptoms include nausea, vomiting, diarrhea, alopecia, fever, and myalgia (8). Occasional anaphylactic reactions have been reported, characteristically at the onset of infusion. Experimental toxicity of Cremophor EL/ethanol in dogs includes hypothermia, tachycardia, lethargy, and retching, which are attributable to the hypotensive effects of Cremophor and the central nervous system depressant effects of ethanol.

The postmortem findings of extensive pulmonary lipid embolism and diffuse alveolar damage account for our patient's symptoms and death. Other clinical diagnoses that were considered include myocardial infarction, pulmonary edema, pulmonary thromboembolism, and sepsis; however, these possibilities were ruled out at autopsy. Anaphylactic reaction was excluded both clinically, by the late onset and character of the symptoms, and by the lack of typical autopsy findings.

Although the drug vehicle Cremophor is suspected of being the source of the lipid emboli in this case, we could not completely exclude endogenous lipid sources. Corticosteroids in particular are known to cause lipid embolism by either of two mechanisms (1–3): destabilization of circulating lipoprotein complexes or induction of hepatic steatosis with release of lipid globules. Our patient's history of corticosteroid therapy could have been predisposing to the formation of intravascular lipid globules by the first mechanism, although this complication does not usually occur at the low dosages she received. The second

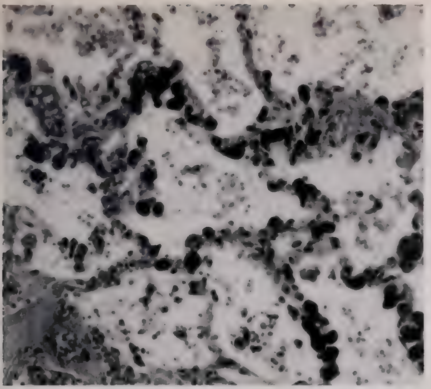

Fig. 2. Lipid emboli within intraalveolar septae and spaces. Osmic acid stain (40× original magnification).

mechanism, which is less common, did not apply in our case because hepatic steatosis was absent. Bone marrow embolism resulting from terminal resuscitative efforts is also unlikely, both because the emboli were devoid of hematopoietic elements and because full-blown diffuse alveolar damage would have required more time to develop.

Interestingly, other lipid emulsions such as Intralipid (a soybean oil extract) that are widely administered and well tolerated at high concentrations have been implicated rarely in incidents of fatal lipid embolism. As in our case, these have involved acutely ill or severely compromised patients (4, 5, 9). A possible basis for this complication is suggested by the experimental finding that some sera with high levels of C-reactive protein can induce the coalescence of emulsified droplets of Intralipid to form lipid globules large enough to lodge in the microvasculature (6, 10). We attempted to ascertain whether a postmortem sample of our patient's serum admixed with various quantities of Cremophor could induce a similar phenomenon, but could find no such effect.

Since fat embolism is not a known complication of Cremophor administration despite the frequent use of this vehicle, we must conclude that our case represents an isolated and unusual incident. Although its cause remains unclear, the patient's severely compromised pulmonary function, and perhaps the concurrent administration of steroids, may have been important predisposing factors. Caution should be used in the administration of this agent to patients with compromised pulmonary status.

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Lumpy Jaw due to *Actinomyces meyerii*: Report of the First Case and Review of The Literature

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Abstract

Actinomyces are normal oral commensals that infrequently cause disease in humans. The species *Actinomyces meyerii* has been described in only five previous case reports, and never as being the etiologic agent in cervicofacial disease (lumpy jaw). This report, written by the patient, depicts the first known case of cervicofacial actinomycosis secondary to *A. meyerii* and reviews the world literature on this organism.

The following case study is unusual in two respects. First, it affords the opportunity for the patient, then a fourth-year medical student, to be able to write up his own case. Second, *Actinomyces meyerii* as the etiologic agent in cervicofacial actinomycosis has not been previously reported.

Case Report. A previously healthy 24-year-old white man underwent routine extraction of an impacted left lower wisdom tooth using local anesthesia. He was given a one-week course of penicillin (250 mg four times a day) postoperatively and did well until two weeks later, when he noticed swelling and discomfort in the left submandibular region. Reexploration revealed no gross pathology, and he was again placed on a one-week regimen of penicillin therapy. The pain and swelling continued and were monitored weekly by the oral surgeon, who entertained the diagnosis of sialoadenitis.

After approximately six weeks, an area of fluctuance was noted, and the patient was referred to a general surgeon. Aspiration revealed frank pus; after incision and drainage of the abscess, the patient was treated with dicloxacillin for presumed staphylococcal infection. A culture taken at that time (aerobic only) subsequently showed no growth, but treatment continued with a 2½-week course of dicloxacillin (250 mg four times a day). Within two days after the antibiotic had been discontinued, another area of induration, erythema, tenderness, and fluctuance developed in the left submandibular region, adjacent to the first incision. This was reincised and the patient was again treated with dicloxacillin pending repeat culture results. By the next morning the wound was no longer draining well, so the patient sought consultation with an infectious diseases specialist. A Gram stain was immediately taken, revealing filamentous gram-positive branching rods, and the patient was subsequently admitted to the hospital.

Physical examination disclosed a 3×4 cm firm, erythematous, fluctuant, tender mass in the left submandibular region (Fig.). No sinus tracts were evident. The patient was afebrile, and the rest of the examination was entirely negative. Admission laboratory values were all within normal limits, including a white-blood-cell count of 9,100/mm^3 without shift and an erythrocyte sedimentation rate of 3 mm/hour. Multiple dental films and a panorex of the mandible showed no evidence of bony involvement.

The patient subsequently underwent surgical incision and drainage with débridement of

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necrotic material. Findings at surgery were described as small amounts of pus and necrotic debris, with the surrounding tissues being woody and edematous. Pathologic evaluation revealed granulation tissue with both acute and chronic inflammatory cells; no sulfur granules were seen. Anaerobic cultures grew out *A. meyerii;* all other cultures and special stains were negative.

The patient was placed on an antibiotic regimen consisting of a three-week course of high-dose intravenous penicillin (18 million units daily) followed by a nine-month course of oral penicillin VK (2 gm/day). Four years after therapy the patient has no complications or evidence of recurrence.

Discussion. Actinomyces are anaerobic gram-positive endogenous bacteria that are part of the normal oral flora. Owing to their slow growth and tendency for branching, they were at first classified as fungi, but lack of a nuclear membrane and chitin in their cell wall, as well as reproduction by fission and inhibition by antibiotics and not amphotericin B, led to their recategorization as true bacteria (1). The three major clinical manifestations of actinomycosis are cervicofacial, thoracic, and abdominal-pelvic; however, primary disease has also been reported in the central nervous system, orbit, paranasal sinuses, and scalp (2). Infection, which shows a 3:1 male predominance, can affect any age group (1). Often other bacteria are associated with the actinomyces, but their role remains unclear.

Cervicofacial actinomycosis, also known as lumpy jaw, accounts for 50%–60% of all cases (3) and has two different clinical patterns. The more common pattern is a slow-growing, painless, fluctuant swelling at the base of the mandible. However, it can also be manifest as an acute, painful submandibular mass simulating a pyogenic infection. Sinus tract formation to external or internal mucosal surfaces is common, as is the presence of sulfur granules, which represent conglomerates of the bacteria itself. Because actinomyces are conventionally saprophytic organisms, there must be some sort of break in the normal mucosal barriers for them to cause infection. Thus, cervicofacial disease usually occurs after dental manipulation or trauma, which allows the oral commensal bacteria to invade the local soft tissues. Once infection is initiated, it spreads without regard to facial tissue planes and forms suppurative masses. It is thought that trauma may affect the oxygen supply and thus produce an environment more favorable for these anaerobic organisms (4).

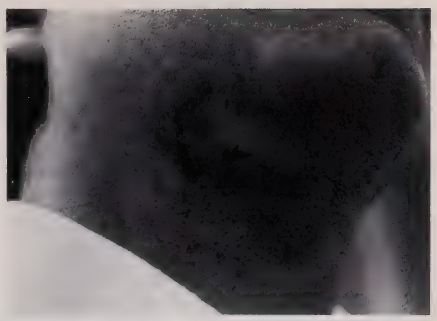

Fig. Left submandibular abscess after two unsuccessful incisions and drainage.

Diagnosis of actinomycosis is made by the typical-appearing Gram stain of filamentous gram-positive branching rods and subsequent growth in anaerobic culture, or by histopathologic presence of typical sulfur granules. Treatment consists of local surgical drainage of abscesses and excision of sinus tracts, followed by a prolonged course of antibiotic therapy. The exact route, duration, and even chemotherapeutic agent are debatable; however, a consensus sanctions several weeks of high-dose intravenous penicillin followed by several months of oral penicillin.

There are six distinct species of the genus *Actinomyces: A. israelii, A. naeslundi, A. odontolyticus, A. viscosus, A. meyerii,* and *A. bovis.* They can be distinguished from one another by colony morphology, ability to grow aerobically, biochemical testing, and sugar fermentation results. *A. israelii* is by far the most common etiology of human actinomycosis, but all species can be found as part of the normal oral-pharyngeal flora, with the exception of *A. bovis,* which has only been isolated from animals.

A. meyerii, the causative agent in this case report, is characterized as follows (5): strictly anaerobic (as opposed to the other species, which demonstrate variable aerobic growth); form smooth, raised, convex colonies, off-white to gray; catalase, esculin, and arginine negative; nitrate and methyl red positive; ability to ferment galactose, xylose, glucose, ribose, and lactose, but not mannose or raffinose. *A. meyerii* was first isolated by K. Meyer in 1911 from a pulmonary empyema, but was called a *Streptothrix* (6). In 1956 A. Prevot isolated the same organism, along with

TABLE

Case Reports of Clinical Disease Associated with Actinomyces meyerii

Case	Author (Date)	Patient Age/sex	Site of infection	Associated organisms	Treatment	Outcome
1	Lipton & Sonnenfeld (1980)	50/M	Osteomyelitis, right tibia	*Bacteroides* sp *Streptococcus mitis*	Sequestrectomy; i.v. PCN, 21 million units/day for 1 wk, then p.o. PCN, 1.5 gr/day, for 4 mos	Clinical cure, 1-yr follow-up
2	Rose et al. (1982)	49/M	Thoracic; chest wall abscess	*Actinobacillus actinomycetemcomitans* *Bacteroides ureolyticus*	i.v. clindamycin, 2.4 gr/day for 4 wks, then p.o. tetracycline, 2 gr/day for 6 mos	Death—empyema developed; patient died from respiratory failure
3	Rose et al. (1982)	62/M	Thoracic; metastatic abscess to left hip	*Fusobacterium nucleatum*	Chest tube drainage; i.v. PCN, 12 million units/day for 5 wks, then p.o. PCN, 2 gr/day for 12 mos	Unknown
4	Rippon & Kathuria (1983/84)	55/M	Thoracic	*Eikenella corrodens*	Left-upper-lobe lobectomy	Unknown
5	Dijkmans et al. (1984)	28/F	Central nervous system, brain abscess	*Streptobacillus moniliformis*	i.v. PCN, 36 million units/day for 2 mos; ventriculocardiac drain	Clinical cure, 1-year follow-up
6	Pordy (1988)	24/M	Cervicofacial	None	Surgical debridement; i.v. PCN, 18 million, units/day for 3 wks, then p.o. PCN, 2 gr/day for 9 mos	Clinical cure, 4-yr follow-up

i.v. = intravenous; p.o. = by mouth; PCN = penicillin.

other bacteria, from a wound abscess and listed it as *Actinobacterium meyerii* (6). In 1977 Holderman et al reclassified this organism in the genus *Actinomyces*, with the specific epithet *meyerii* (6, 7).

A review of the literature revealed only four articles (6–10) describing five case reports of clinical disease associated with *A. meyerii* (Table). Three of the patients reported in the literature were diagnosed as having thoracic actinomycosis, one had osteomyelitis of the tibia, and the fifth patient had a brain abscess. In all five previously reported cases the infection was polymicrobic, *A. meyerii* being isolated in conjunction with other bacteria. Chemotherapeutic treatment consisted of initial high-dose intravenous penicillin or clindamycin, usually followed by long-term penicillin or tetracycline use. Four of the patients had some sort of surgical procedure done; one patient had surgical resection alone without any concomitant antibiotic therapy. Of the three cases where long-term follow-up was available, two did well after one year, and the third died from a complication of his disease.

The case presented in this paper is typical for cervicofacial actinomycosis, the major exception being the etiologic species. It occurred after dental manipulation and developed very slowly, taking several months for a frank abscess to manifest. The delay in diagnosis is also characteristic and reinforces the need for this organism to be included in the differential diagnosis of cervicofacial infections; thus anaerobic cultures must be taken. The lack of response to the initial oral antibiotics is not surprising, given that high-dose, long-term therapy is usually required and that semisynthetic penicillins, such as dicloxacillin, are not active in vitro against actinomyces (10). Appropriate treatment, which cured this patient, results in a cure rate over 90% (11).

What makes this case unique is that it is the first and only known reported description of cervicofacial actinomycosis being caused by *A. meyerii*. Also, unlike the five cases previously reported, this is the only one in which *A. meyerii* was the sole organism recovered from culture, confirming that this bacterium was indeed the responsible pathogen. In contrast, Dijkmans et al (9) question the clinical significance of the *A. meyerii* isolated and Lipton and Sonnenfeld (8) query the primary or secondary nature of the actinomyces.

The explanation for the sparsity of reports on *A. meyerii* causing clinical infection is not known. One possibility is that whereas *A. israelii* can be isolated from 30%–50% of properly cultured dental surfaces, saliva, and tonsillar crypts (1), perhaps *A. meyerii* is less frequently an oral commensal. Alternatively, the explanation may be that only recently have microbiology laboratories been able to accurately speciate the genus *Actinomyces*, or that *A. meyerii*'s strict anaerobic requirements have inhibited identification.

In summary: *A. meyerii* is an uncommon cause of human infection, but this case broadens the realm of clinical disease this organism is capable of producing.

Acknowledgments

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Septic Complications of Procainamide-Induced Agranulocytosis: Report of Two Cases

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Abstract

Two patients in the eighth decade of life developed agranulocytosis on procainamide therapy. Both had a septic complication as a result and responded to withdrawal of the drug and aggressive medical and surgical therapy. Agranulocytosis is a known complication of the use of procainamide. The proposed mechanism of this drug-induced complication is discussed, and prior reported cases are reviewed.

Repeated use of procainamide has occasionally resulted in agranulocytosis and death. The first patient reported, in 1951 by Inouye, Millar, and Townsend (1), succumbed to procainamide-induced agranulocytosis. Since that time, only a small number of cases have appeared in the literature. Because procainamide is effective and frequently used as a cardiac antiarrhythmic agent, the physician must be aware of this potentially lethal complication. Two cases of agranulocytosis with sepsis are presented along with a brief review of the literature.

Case Reports

Case 1. In June 1987, a 78-year-old man was admitted after two days of chest pain. Medications on admission included propranolol, erythrityl tetranitrate, and nylidrin. On examination the patient demonstrated blood pressure 170/90 mm Hg, a regular pulse of 60/min, and a grade II/VI systolic apical murmur. Other findings were normal. Complete blood count revealed hemoglobin of 15.3 gm% and white blood cell count of 7800 cells/cc with a normal differential. Blood urea nitrogen, creatinine, and liver function findings were normal. Immediately after admission, the patient developed supraventricular tachycardia, progressing to ventricular fibrillation and cardiac arrest. Resuscitation was successful. Treatment was started with procainamide, 250 mg every 6 hr orally. Propranolol was discontinued. Electrocardiographic evidence of an inferolateral myocardial infarct evolved. Cardiac enzyme elevation was noted. The patient had a stormy course over the next six weeks with recurrent arrhythmias.

During the sixth week of hospitalization the white blood cell count was reported as 3200 cells/cc with 40% granulocytes. Six days later the patient developed a temperature of 104°F. Multiple blood cultures grew *Escherichia coli*. The white blood cell count fell to 1200 cells/cc, and gentamicin, 80 mg every 8 hr, was given intravenously. Hematologic consultation recommended discontinuance of the procainamide after bone marrow aspiration was normal except for complete absence of granulocytes. The source of the sepsis was identified as a necrotizing perianal infection secondary to a thrombosed external hemorrhoid. Blood levels of procainamide were not available. Lupus erythematosus and antinuclear antibody studies were negative. The patient evidenced no further arrhythmias and did not require further antiarrythmic therapy. During the

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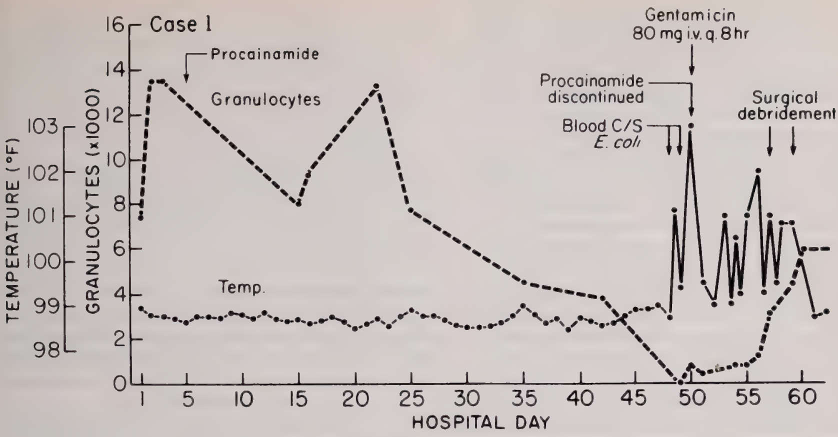

Fig. 1. Course of procainamide-induced agranulocytosis, Case 1.

10 days following the withdrawal of procainamide, the patient's granulocyte count rose to 6000 cells/cc and his perianal wound shortly healed with debridement of necrotic tissue. The patient was subsequently discharged (Fig. 1).

Case 2. In January 1980, a 73-year-old woman was admitted to Long Beach Memorial Hospital with a temperature of 104°F and marked difficulty in swallowing. Medications on admission included chlorpropamide, digoxin, and chlorthiazide. The patient had had right cerebral thrombosis many years before without residual deficit and a recent right cerebrovascular accident with residual left hemiparesis. A permanent pacemaker had been placed two years before for sick sinus syndrome. The patient had been treated with quinidine 6 months before, but thrombocytopenia necessitated discontinuance of this medication. Platelet count subsequently returned to normal levels. Three months before, treatment with procainamide, 250 mg every 6 hr, was started for multiple ventricular premature contractions. Four and eight weeks after initiation of procainamide therapy, routine blood count and platelet counts were normal. On the day of admission the patient had a temperature of 104°F, ulcers on the soft palate, and severe pharyngitis. There was a grade II/VI systolic ejection murmur and the cardiac rhythm was irregular. The liver and spleen were not palpable. Complete blood count showed hemoglobin of 11.7 gm% and white blood cell count of 700 cells/cc, the peripheral smear demonstrating the presence only of lymphocytes. Hepatic and renal function tests were normal. Procainamide serum levels were not available.

Procainamide was discontinued; aqueous penicillin, 2 million units every 4 hr, and gentamicin, 40 mg every 8 hr, were started intravenously. Bone marrow aspiration revealed agranulocytosis. Blood cultures were later reported as growing *Pseudomonas aeruginosa.*

Seven days after discontinuance of procainamide, polymorphonuclear cells were identified on the peripheral smear and the pharyngitis began to resolve. The white blood cell count returned to normal over the next week, and the patient was discharged with a white blood cell count of 9,600 cells/cc with a normal differential.

Discussion

Agranulocytosis is now a recognized complication of procainamide therapy. Other adverse effects include urticaria, gastrointestinal complaints, chills, fever, and a syndrome resembling lupus erythematosis. Although fewer than 20 cases (1–17) of procainamide-induced agranulocytosis have been reported, the exact incidence of this phenomenon is unknown. The number of reported cases has doubled in the last decade, either because of more widespread use of the drug or because of better recognition of this adverse effect.

Review of the English-language literature reveals certain common features in patients developing agranulocytosis secondary to procainamide (Fig. 2). The majority of patients (75%) survived; the mean age was 64 years; there was no sex predilection. Although there was a definite increase in the complication as patients received more drug over longer periods, as little as 36.5 gm was enough to cause agranulocytosis. One point should be noted: the total dose of the drug in patients developing agranulocytosis did not determine survival. A patient who had received only 42 gm of procainamide succumbed to infection secondary to agranulocytosis, whereas a patient who had received 350 gm recovered.

Procainamide is normally excreted by the kidney, the half-life being approximately 3–4 hr. About 40%–70% is excreted unchanged; the remainder is biotransformed in the liver, predominantly by *N*-acetylation. Giardina et al (18) demonstrated that the main excretory products are unaltered procainamide and *N*-acetyl procainamide (NAPA), 73%–91% of a given dose being found in the urine within 72 hr as these substances; however, at least two other metabolites are present that have not been identified. Acetylor phenotype (slow or rapid acetylation) is genetically determined and modifies the amount of hepatic acetylation. Failing renal function also plays a role, increasing hepatic metabolism of procainamide. The acetylated metabolite NAPA has pharmacologic activity similar to that of the parent compound and undoubtedly contributes to the antiarrhythmic activity of the drug (19). The therapeutic range of procainamide is usually given as 4–8 μg/ml. However, Drager et al (20) suggest that measurements of the levels of NAPA as well as procainamide are needed to establish safe ranges for both active compounds and avoid the possible additive toxic side effects of both.

There seems to be a sequence of events in cases of procainamide-induced agranulocytosis: exposure to the drug, recognition by the target organ, leukocyte maturation, arrest, fall in peripheral granulocyte count, sepsis, and death. Although few patients go on to die, overwhelming infection and subsequent reversal of the phenomenon after withdrawal of the drug is unpredictable. The reproducibility of the agranulocytosis was documented by Konttinen and Tuominen (9), who demonstrated a second episode following reexposure to the drug after a complete hematologic remission.

The exact mechanism by which procainamide causes agranulocytosis is not known. It has been suggested that slow acetylators (increased procainamide-to-NAPA ratio) are more prone to the drug-induced side effects (21), but this has not been confirmed. Procainamide does not appear to cause agranulocytosis through an immunologic mechanism, which is thought to be the mechanism in its production of a lupus-like syndrome (22). Leukocyte agglutinins have never been found in patients with agranulocytosis, strongly suggesting that there is no immunologic basis for this adverse side effect.

	SURVIVAL %	MEAN AGE	SEX	DOSE RESULTING IN AGRANULOCYTOSIS (gm)	MEAN DURATION OF THERAPY (Days)	
					Survivors	Mortalities
PRIOR CASES	75	63.9	M=F	36.5 - 316.3	38	65
CASE 1	Yes	78	M	38.75	49	
CASE 2	Yes	73	F	90	90	

Fig. 2. Comparison of 2 cases presented here and prior reports.

Prisciotta and Kaldahl (23) have conducted studies that demonstrated that certain drugs (chlorpromazine) partially inhibit nucleic acid incorporation into DNA and therefore cause leukocyte maturation arrest in the marrow. It has been hypothesized that procainamide may have a similar effect in interfering with DNA production in developing granulocytes, with resultant agranulocytosis.

As previously described, neither specific dose or duration of therapy of procainamide nor age or sex of the patient will give a clue to individuals who will develop procainamide-induced agranulocytosis. In a study by Lawson and Jick (24) of 488 hospitalized patients receiving procainamide, 45 had an adverse reaction to the drug, but not one developed agranulocytosis.

The patient and the physician should be aware of specific signs and symptoms before initiating treatment with the drug. First, the patient's general condition should be evaluated. The medication should be used with caution in patients with hepatic or renal disease and in those with histories of prior drug hypersensitivity (as in Case 2). Quinidine therapy has resulted in thrombocytopenia. Certain side effects should alert the patient to the need for medical attention: fever, fatigue, mental confusion, sore throat or gums, diarrhea, anorexia, and vomiting. Regular visits to the physician to check the progress of therapy are recommended. Monitoring of the granulocyte count monthly in the first 3 months of therapy (almost all cases of agranulocytosis are reported in this period) will identify patients with falling granulocyte counts.

Once a patient with agranulocytosis is identified, all drugs with this side effect should be discontinued. If the patient's granulocyte count falls below 1000 cells/cc, reverse isolation should be instituted. Antibiotics are utilized only if there is evidence of sepsis. If sepsis is present, appropriate antibiotics are begun. A diligent search for the source of the infection is undertaken, and if a surgically correctable lesion is found, adequate drainage and debridement are performed. In fulminant disease, leukocyte transfusions are indicated. Steroids may or may not have a role in reversal of the bone marrow maturation arrest. Since there is no specific way to identify the patients at risk, administration of procainamide should be limited to patients who have absolute indications for use of the drug. Early detection and treatment are the major goals in the event of procainamide-induced agranulocytosis.

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Adenolipoma of the Thyroid Gland

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Abstract

Mature adipose tissue within the parenchyma of the thyroid gland is unusual, occurring in two forms: the relatively more common diffuse adenolipomatosis and the very rare circumscribed adenolipoma. The case reported here was characterized by at least three distinct adenolipomas which were part of a large multinodular goiter. We found only five definite cases of adenolipoma of the thyroid in the literature. The pathogenesis of this entity is uncertain; although the favored hypothesis is development from adipose tissue incorporated within the gland during embryogenesis, the theory of adipose metaplasia of the stromal mesenchymal cells appears absolutely tenable as well.

Case Report. A 76-year-old woman was hospitalized because of increasing stridor, hoarseness, and dyspnea. She had an enlarging goiter of at least 10 years' duration, treated with 0.1 mg levothyroxine daily. She also had a history of diabetes mellitus, hypertension, mild congestive heart failure, and chronic renal insufficiency. Physical examination revealed an obese woman in mild respiratory distress with a massive swelling of the anterior aspect of the neck. The mass was fluctuant, mobile, and nontender. There was a sonorous stridor. The physical findings were otherwise unremarkable. A computerized-tomography scan of the neck revealed bilateral, nonhomogeneous, and focally cystic and calcified masses, with narrowing of the trachea. Thyroxine level was 11.7 μg/100 ml (nl 4.5–11.5), triiodothyronine resin uptake 42% (nl 30%–40%), free thyroxine index 4.9 (normal 1.7–3.9), and TSH 0.0 IU/ml (nl 0.0–5.0). Total thyroidectomy and tracheostomy were performed. The patient was discharged after a prolonged postoperative course due to her concomitant medical problems.

Pathologic Findings. The specimen consisted of a markedly enlarged thyroid, weighing 410 gm, each lobe measuring 11 cm in the largest diameter. The parenchyma was dark brown and nodular throughout and showed areas of hemorrhage, calcification, and colloid-filled cysts. Extensive sectioning of the specimen revealed three nodules, all at the periphery of the right lobe, which differed from the rest of the goiter. They measured from 1 to 3.5 cm in size, were solid, soft, yellow and hemorrhagic or brown, did not appear to contain any colloid, and enucleated easily during the dissection (Fig. 1). Microscopically they revealed an intimate mixture of mature adipocytes and thyroid follicles (Fig. 2). The latter were of various sizes and were often compressed by the adjacent fat cells (a "thumbprint"-like appearance) (Fig. 3). There was no evidence of lymphocytic infiltrates or amyloid. The thyrolipomatous nodules were surrounded by a thin fibrous capsule. Multiple calcium oxalate crystals were seen within the colloid of the adenolipomas and in the nodules of the goiter. The remainder of the specimen showed the usual features of a multinodular goiter with degenerative changes.

Discussion. Although rare fat cells are occasionally seen within the connective tissue septa of the thyroid gland, the occurrence of large fat-cell aggregates in this gland is distinctly uncommon. The diffuse adenolipomatosis can be associated with a colloid goiter (1–5), sometimes with heavy lymphocytic infiltrates (6–9) or vascular and

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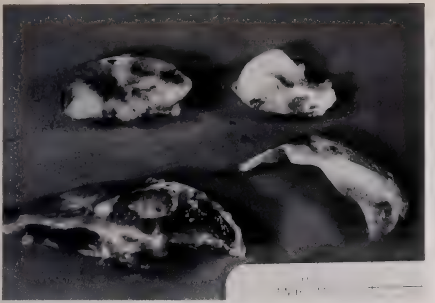


Fig. 1. Gross appearance of adenolipomas (two upper sections are of same tumor).

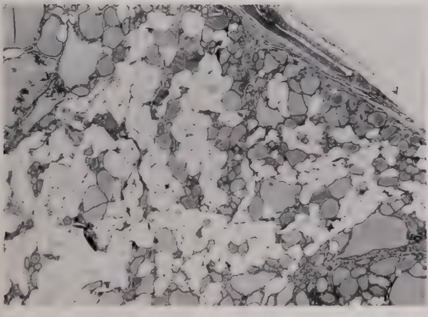
stromal deposits of amyloid (1, 2, 10). A well-circumscribed adenolipoma of the thyroid (thyrolipoma), however, remains a rara avis; only five instances are on record, to the best of our knowledge (11–14). These previously reported cases represented solitary lesions in otherwise normal thyroid glands. Interestingly, in one of these cases the patient had associated lipomas of the thymus and the larynx (13).

Our patient was euthyroid, as were the earlier reported cases of adenolipoma and adenolipomatosis of the thyroid gland. Indeed, these lesions appear to be nonfunctional, as opposed to some adenolipomas of the parathyroid (15) and symptomatic thymolipomas (16).

The thumbprint compression of the follicles by adjacent adipocytes has not been mentioned in prior histologic descriptions of the thyrolipomas. The compression might indicate relatively recent and active proliferation of the fat cells within the thyroid, although we could not find mitotic activity of these cells.

The etiology of the adenolipoma or adenolipomatosis of the thyroid remains controversial. Fatty infiltration has not been described as part of the spectrum of degenerative changes in a colloid goiter, such as hemorrhage, calcification, and ossification. There seems to be no relationship between adiposity of the thyroid and age or nutritional status of the patient (3). One possible explanation for the presence of fat cells in the hyperplastic goiter might be simply an invasion of the adjacent fatty tissue of the neck by the hyperplastic thyroid, with eventual incorporation of the fat cells into the substance of the goiter. However, in view of the relative frequency of the adenomatous goiter and the rarity of thyrolipomas, we consider this possibility rather unlikely. Careful gross examination of the specimens with multiple sections from the suspicious areas might, however, uncover more cases of the thyrolipomas.

The two accepted hypotheses are (a) inclusion of fat cells within the thyroid substance during embryogenesis of the organ and (b) mesenchymal metaplasia. The first theory is similar to that explaining the presence of striated muscle in the thyroid (17). The second hypothesis, fatty metaplasia of the thyroid stroma (18), seems to have light microscopic and ultrastructural evidence, as described by Bettendorf et al (4). The recently reported case of a papillary carcinoma of the thyroid with lipomatous stroma (19) appears to us to support the possibility of the metaplastic theory as well.



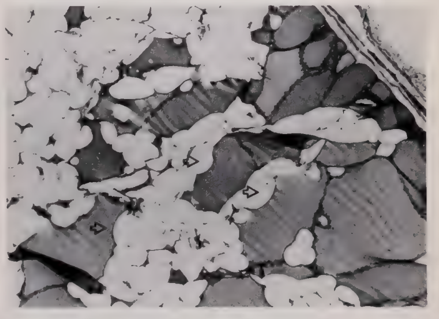


Fig. 2. **Left** Low magnification of adenolipoma demarcated by fibrous capsule (H&E ×40 original magnification). Fig. 3. **Right** Higher magnification, showing mature fat cells intermingled with thyroid follicles. Note thumbprint compression of colloid by adjacent fat cells (arrows) (H&E ×100 original magnification).

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Student Corner

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Surgery in an Era of Constrained Resources

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The end of the 20th century has proven to be a period of tightly constrained resources in all areas of the domestic service economy of the United States. With medical expenditures currently exceeding 10% of the gross national product, health care has become one of the principal targets for cost containment.

The federal government has already begun to drastically slash discretionary expenditures in the health care field, to limit or "cap" its responsibility for increases in state Medicaid expenditures, and to search for ways to limit its responsibility for cost increases under Medicare. With budgetary problems on the rise, even further reductions in federal and state support can be anticipated, resulting in decreased eligibility and benefits.

Private industry and major unions, likewise, after decades of indifference to cost rises for health care, are beginning to scrutinize their expanding expenses for health care benefits. Their interest in information on what services they are getting for their health care dollars has exploded.

The provision of surgical care has for the first time come under systematic scrutiny by health policy researchers. Their critical findings, in a continuing era of constrained resources, will be utilized to challenge the surgical profession on economic and quality issues.

The purpose here is twofold: to briefly review the key studies of surgical care that will affect the coming debates, and to suggest and evaluate some of the specific ways in which surgeons can improve the efficiency of their practices with perhaps an improvement in quality of care.

Literature Review

The external world is raising three key questions with increasing frequency and in greater detail with the surgical community. In turn, the surgical community must pose these questions to itself in order to find solutions to the problems that will confront it during the coming decade. The first question is whether significant underprovision and overprovision of surgical services exists in areas of the United States. If so, what forces are responsible? Second, are surgeons within a given specialty providing reasonably equivalent quality of care for surgical procedures, and are the hospitals in which they practice equivalent in surgical results, for similar patients? If not, what are the limits of variation in quality that should be permissible? Third, how efficient is the current system in the performance of surgery? In times of constrained resources, can equivalent value in surgical results be achieved with less human or capital resources? Some key studies of these questions of quantity, quality, and efficiency of surgical services in the United States are discussed.

Volume of Surgical Services. The central research question for the U.S. surgical community is: "Is excessive surgery being performed in some areas of this country?" Most studies in the last 20 years conclude with answers that range from "probably" to "definitely." Although the evidence is not conclusive, enough studies have produced similar findings to justify serious concern by policy makers and researchers.

The earliest gun in the current attack on the issue of excess surgery was fired in 1952 with

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Lembcke's study of the incidence of appendectomy in 23 hospital areas in and around Rochester, New York (1). Calculated rates varied threefold. In some areas with high rates, it was found that the majority of appendectomies were performed by a minority of surgeons, suggesting that in areas in which hospital operations are not strictly controlled, the simple fact of greater accessibility to medical care is the deciding factor.

In 1969–70, a pair of special articles examining variation in rates of surgery appeared. Lewis assessed rates of six common surgical procedures in 11 hospital districts of Kansas (2). Three- to fourfold variations were found. This study was followed by Bunker's comparison of rates of surgery in the United States, England, and Wales, a study that also noted large differences in surgical rates (3). Both studies demonstrated that differences in the rate of procedures paralleled the ratios of surgical manpower and number of hospital beds to the population served, and suggested that patient admissions for surgery expand to fill beds, operating suites, and surgeons' time.

In the following decade, many studies looked at geographic variations in the rates of utilization of surgical care. The hypothesis common to all was that if one adjusted for differences in patients' need and if resources were in sufficient supply, rates of surgery from one area to another should be approximately equivalent. Case studies of variation between hospital service areas in Vermont (4), the Canadian provinces (5), Maine (6), Wisconsin (7), and other locales repeatedly showed two- and threefold and even higher variation in surgical rates for defined populations.

Mitchell and Cromwell (8) in 1980 completed the first national study of variations in surgery among defined small geographic areas; their database was the entire National Health Interview Survey from 1969 to 1976, with detailed interviews of people in 350 of 1,900 census primary sampling units in the United States. Total surgery rates varied from 11 to 153 operations per 1,000, with equal numbers of areas above and below one standard deviation of the mean. Elective surgery rates varied even more widely; one of every six areas experienced rates more than 50% higher than the mean.

Multivariate cross-sectional and time series analyses were undertaken to determine whether differences in rates could be explained by underlying differences in the population, in the surgical community, or in the health care system. After controlling for the supply of surgeons and health system supply factors, the model explained only 9% of the variation in elective surgical rates. Thus, the wide variations that were obtained, in large part, do not appear to be due to the underlying basic social, economic, or demographic factors, or to patient needs in an area.

Clearly, there is no easy solution to the problems presented by these results. If the national means were to be accepted as optimal levels, there are not only substantial problems of overuse, but also some very serious underservice problems. A higher optimum would mean that in many areas of the United States patients are not receiving enough surgical care, despite the large total number of surgeons in practice. On the other hand, a lower optimum level would mean that the majority of the population is undergoing excessive surgical procedures. Certainly, this degree of geographic variation leaves many analysts with a concern that in some areas either too much or too little surgery is being performed, although they cannot evaluate which is the case. Perhaps one ought to focus instead on the quality of care and the health care outcome.

Quality of Care. For most of this century, once a hospital was licensed to have a surgical service and a physician with a license was granted privileges to practice surgery at a hospital, the working assumption was that all providers could achieve approximately equivalent results and outcomes for standard surgical procedures. It was common wisdom that for any given procedure, a handful of famous specialists or surgical clinics achieved more excellent results. Yet the popular perception, both inside and outside the profession, was that most institutions could provide reasonably comparable results for the same mix of patients undergoing standard surgical procedures. These assumptions are now being questioned.

In 1976, the Stanford Center for Health Services Research released the findings of its Institutional Differences Study, an examination of variations in postsurgical morbidity and death for 14 surgical procedures based on data for 314,000 patients at 1,224 hospitals (9). The observed-to-expected mortality levels varied by a ratio of more than two to one.

Shortly thereafter, in 1979, Luft, Bunker, and Enthoven reported major differences in surgical mortality rates in relationship to surgical volume (10). An inverse relationship of actual to expected death rates versus annual volume of procedures was found for 10–12 procedures studied. Of the 162,569 cases evaluated, these authors estimated that there were over 3,000 "excess" deaths.

A similar inverse relationship between surgical volume and incidence of postoperative wound infections was reported in 1981 by Farber, Kaizer, and Wenzel (11). Hospitals with large rates of surgery for a particular operation have lower infection rates. A high total volume of surgery at an institution did not appear to protect against higher infection rates if the volume was low for a specific operation.

These studies tend to indicate that there may be systematic and substantive differences in the results of surgical care for common procedures. The differences are so large and the study methods so exhaustive that the conclusions of these studies are not easily refuted. If we accept them, they have profound implications for the public perception of quality of surgical care.

Efficiency of Surgical Practice. The traditional public image of a surgeon is an individual who does several hospital procedures a day, week after week, with occasional night and weekend emergency operations. Studies by Hughes et al (12) and by the National Study on Surgical Service (13) have demonstrated that this view is incorrect. The mean surgical workload of board-certified general surgeons is slightly more than four "equivalent typical operations" a week; however, these averages hide widely unbalanced patterns of surgical activity (for example, more than half of the physicians who perform surgery in the United States actually do less than one hernia-equivalent procedure per week).

Although no direct link has been made between an individual surgeon's volume of a particular procedure and his or her morbidity and mortality results, critics increasingly conjecture that less experience results in worse outcomes. Since this is a proven truth for the hospital, why not for the individual?

The cumulative effect of these studies is to raise a set of difficult issues about the quantity, quality, and efficiency of American surgical care. The study findings will be the context for an increasingly critical barrage of questions posed by analysts of the surgical community. In response, the surgical community can pursue one of two courses. It can attempt to ignore studies that have demonstrated inexplicable variation in rates of procedures and differences in outcomes. Alternatively, it can accept that a serious problem is present and begin to conduct its own review efforts, followed by aggressive corrective actions. The former plan may seem less painful in the short run, but the risk to the surgical profession's autonomy, stature, and economic well-being may be jeopardized.

Ways for Surgeons to Increase Their Efficiency in Using Hospitals

It is critically important for the medical profession to have a constructive role in developing the methods used to control health care costs, so that the methods are consistent with good medical care. Surgeons can make an important contribution by reaching a consensus on treatment routines for common surgical procedures and adopting practices that improve the efficiency of hospital care without compromising its quality. Specific ways in which surgeons can decrease their use of the hospital and its technology by reassessing their routines are explored below.

Indications for Surgery. One major factor responsible for the wide variations in surgical rates is the surgical socialization that occurs in residency training and clinical-care experiences during the early years of practice (14). If the surgical community recognizes the need to reduce small area variations, some narrowing of the currently wide range of indications for surgery being advocated will be necessary. The development and dissemination of guidelines on acceptable indications for commonly performed operations ought to be pursued as a means to educate physicians, thereby eliminating some of the unnecessary procedures currently being performed.

Evidence suggesting that high surgical rates can be modified by informational and educational programs comes from a study on the effect of outside surveillance on the rate of hysterectomies in Saskatchewan (15). An advisory committee of physicians compiled a list of indications for hysterectomy, and five hospitals were reviewed before and four years after the surveillance program was implemented. The total number of hysterectomies in the province dropped 32% in the intervening four years, and the proportion of "unjustified" procedures, as defined by the advisory committee, dropped from 23.7% to 7.8%. A similar study by Wennberg et al (16) demonstrated that informational programs on the appropriate indications for tonsillectomy, aimed at physicians practicing in areas with a high number of procedures, can reduce the tonsillectomy rate.

The development of a standardized set of acceptable indications for common surgical procedures would provide the basis for monitoring the results of a program designed to eliminate unneeded admissions. In a cost-containment milieu, surgeons whose cases do not fit consensus criteria may feel pressure to justify their admitting patterns. Clearly, progress will depend on agreement among senior and respected surgeons concerning the indications for surgery, on dissemination of the findings of these groups to local surgeons, and ultimately on a change in physician behavior with regard to the decision of when to operate.

Length of Stay. Little attention has been given to the few published papers that demonstrate good results for common surgical procedures followed by shorter-than-usual hospitalization periods. Although there may be some cost-savings potential in the attempt to curb "outlier" activity, in which patients with excessive lengths of stay for uncomplicated surgical cases are identified by peer review, a far bigger goal for cost containment ought to be to find ways to move established norms a moderate amount to achieve greater efficiency while quality is maintained.

Many studies have demonstrated that shorter lengths of stay are possible with quality of care maintained. The work of Lindgren et al (17) in Sweden indicates a 25% decrease in the average stay for cholecystectomy between 1955 and 1965, and another 25% decrease between 1965 and 1975. Clark (18) has demonstrated that in a series of 82 consecutive thyroidectomy patients, it was possible to discharge 96% within four days after surgery and 94% after three days, with little morbidity and no mortality; this stay is several days shorter than the U.S. average for thyroidectomy. Tomatis and co-workers (19) have shown that patients undergoing coronary artery bypass surgery can leave on the fifth day postoperatively, instead of remaining hospitalized for seven or more days, which has been the standard practice in many institutions.

It appears that surgeons can make major contributions to better cost management by reassessing the length-of-stay protocols for common surgical procedures and by making revised suggestions available to local communities that are interested in cost containment. Such guidelines should not be mandatory for all cases, since there will continue to be important exceptions—patients who are more sick than is usual for a certain procedure. But there is little reason to continue to regard as acceptable the very wide range of routine preoperative and postoperative length of stay for frequently performed surgical procedures.

Yet, if shorter lengths of stay can be achieved and if quality can be maintained for frequently performed surgical procedures such as cholecystectomy, thyroidectomy, and open-heart surgery, why is more activity not devoted to this goal? The most likely reason is that in the past, concentrating on possible economies in surgical practice has not been seen as serving a purpose. As Simpson has stated: "The range of length of stay for particular conditions . . . results as much from force of habit or perverse necessity as from considered judgement" (20). Until recently, little incentive existed for the surgical profession to examine these issues.

Use of Laboratory Tests. It is now becoming apparent that the use of diagnostic tests and procedures is excessive, and many studies suggest that at least 15%–30% of tests are not useful in diagnosis or treatments (21). This appears to apply to routine batteries of tests as well as to specific diagnostic procedures. Preoperative electrocardiograms, chest x-rays, electrolyte profiles, and other tests as part of the preoperative workup are routine measures now being challenged as having clinical value. In addition, new diagnostic tests may be adopted that preclude the need for other tests commonly performed.

Thus, for a variety of common surgical procedures, established testing routines should be reassessed to eliminate tests that are antiquated or marginally useful. So far, programs to educate house staff in appropriate use of diagnostic tests have resulted in a reduction in use, but unfortunately, once the programs ease, the efficiencies that have been realized are difficult to maintain (22).

Ambulatory Surgery and Admission on Morning of Surgery. Traditionally, the majority of surgical cases have been treated on an inpatient basis. Recently, however, strong evidence has emerged to suggest that a wide range of surgical procedures currently performed in the hospital can be safely and conveniently carried out as ambulatory procedures (23). Indeed, experts have indicated that nearly 30% of all surgery performed in the United States could be performed on an outpatient basis. Yet, despite this evidence, many surgeons appear to be reluctant to move into ambulatory settings even for cases that have been shown to be appropriate for such settings.

Proven advantages to ambulatory surgery for both patient and surgeon include (a) early ambulation and return to work (24), (b) less medication pre- and postoperatively (25), (c) decreased postoperative complications caused by being inactive and in a hospital, (d) reduction of psychological stress associated with hospitalization, (e) reduced bed congestion, (f) more effective use of physicians' time, and (g) cost decreased by at least $200 per procedure (26).

Problems and possible disadvantages of ambulatory surgery include (a) patient resistance, expressed in comments such as "My friends were always hospitalized for a D-and-C, why shouldn't I be?" (b) physician resistance, stemming from force of habit, lack of community acceptance, lack of immediate availability of care in case of complication, and (c) potentially decreased hospital income.

Incentives for performing ambulatory surgery are relatively new, spurred by alterations in hospital and physician reimbursement. Acceptance by physicians of the concept of ambulatory surgery is increasing slowly but steadily in spite of the many pressures to avoid "come-and-go" surgery; in 1977 only 45% of hospitals in the United States had programs for ambulatory surgery, but by 1980, this proportion had increased to over 50% (26).

Should all hospitals embark on or enlarge a program of ambulatory surgery? Ambulatory surgery should be tailored to meet the needs of the community, often expressed by the degree of acceptance by patients and physicians. Also, ambulatory surgery should be integrated in a communitywide plan for health services. Nonduplication of facilities must be documented in the planning process, and a balance should be attained between excellent care and minimum cost. If such guidelines are followed, ambulatory surgery can provide more hospital beds for seriously ill patients, reduce waiting time for elective surgery, and reduce average total cost per patient treated at the hospital for the patient, hospital, and community.

A related approach for patients who require only postoperative care is admission to the hospital on the morning of surgery, after appropriate preoperative evaluation as an outpatient. Loop et al (27) advocate this practice for patients undergoing cardiac surgery. They report that in 1982, fully 13.5% of patients who had cardiac surgery at the Cleveland Clinic were admitted on the morning of surgery without apparent adverse effects.

Bashein and Glauber (28) evaluated surgical admissions at University Hospital in Seattle and estimated that 22.6% of the total might have been admitted on the morning of surgery. They conclude: "If one were to extrapolate the 22.6% figure to the estimated 15 million anesthetics administered to adults in the U.S. annually, there is a potential savings of some 3.4 million hospital patient days. If daily room charges average $200, the yearly savings could total a staggering $678 million."

Patient Education. Another poorly recognized yet important approach to reducing hospital costs for surgical cases is increased patient education, particularly preoperative (29). For example, in one study, the anesthesiologist provided information about the surgery and reassurance the night before surgery, and made a brief visit after it (30). Compared with the randomly assigned control patients, the patients in the experimental group reported significantly less pain, requested less postoperative morphine, and were discharged an average of 2.7 days earlier.

Improved patient education also becomes more important as the length of stay is shortened. Because patients in early-discharge programs will need to be particularly knowledgeable in recognizing postoperative complications and be skillful in self-care procedures, such as dressing changes, the education of the patient (and often a family member) will be crucial to the success of such cost-savings programs.

Conclusions

The push by both government and the private sector for increased control over expenses for health care benefits is creating new challenges for the medical and surgical professions. Certainly, costs could be decreased by limiting the size of the medical care "engine," for example, by decreasing the number of hospital beds or controlling the number of expensive technical services. But unless physicians, who control the acceleration and the brake of the medical system, change the speed at which they drive the engine, cost containment will not work.

This paper has argued that surgeons can play a constructive part in the management of health care costs by improving the efficiency of their practices, with no loss and perhaps with an improvement in the quality of care received by their patients. Crucial to the success of all suggestions presented, however, is a change in surgeons' practice behavior, which must come about through education, peer review with feedback, administrative changes, participation, and penalties and rewards.

Thus, the key question becomes: Can surgeons learn to change their behavior to slow the rapidly rising costs of medical care? It is to be hoped that they can and will, because their self-imposed restraint will be the most effective force for ensuring rational cost control while preserving the highest possible quality of care. If for no other reasons, physicians will recognize that their action in limiting further cost increases is the best alternative available—certainly preferable to heavy-handed regulation.

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Student Corner

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Prognostic Significance of Hormone Receptors in Breast Cancer

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Abstract

The prognostic significance of hormone receptors in breast cancer was examined by analyzing data collected prospectively on 625 breast cancer patients at The Mount Sinai Hospital between 1978 and 1984. The influence of the following five factors on disease-free interval was examined: estrogen receptor (ER) level; progesterone receptor (PR) level; extent of axillary lymph node involvement; tumor differentiation; and age of the patient. Although in this study the extent of axillary lymph node involvement was found to be the most important determinant of the disease-free interval, ER status was also highly significant ($p = 0.00098$). When nodal status was accounted for, ER level became the most significant indicator of disease-free interval. PR levels did not enter the model, but this could be attributed to the fact that PR level is highly correlated to ER level ($r = 0.70595$), and hence was already in the model. This study shows ER levels to be significant and independent prognostic indicators of disease-free survival. Women with ER-positive tumors have a longer disease-free survival. The conflicting results reported in the literature indicate that more work needs to be done with longer follow-up periods and more uniform definitions, so that better recommendations can be made to help combat breast cancer.

Breast cancer remains the leading cause of death from cancer among women in the United States today. One of eleven American women will develop breast cancer (1). Research to help diminish the effects of this disease is greatly needed. In this context, I studied the importance of hormone receptors as prognostic indicators for breast cancer.

The question of prognostic significance of hormone receptors in breast cancer is difficult and controversial. One must consider estrogen and progesterone receptors in relation to disease-free interval (DFI) as well as to total survival time.

The literature on estrogen receptors (ER) as prognostic indicators is widely variable and not univocal (Table 1). Many authors report increased survival in women with ER-positive tumors (2–6). Mason et al (4) report that overall survival is significantly influenced by ER status in both node-negative and node-positive patients; in fact, a subgroup of node-negative receptor-negative patients had a significantly poorer survival rate than a node-positive receptor-positive subgroup. Stewart and co-workers (7), however, report no difference in survival between ER-positive and ER-negative patients with operable tumors and lymph node metastases. Aamdal et al (8) find no difference in survival for the first five years, but in a longer follow-up period they see increased survival in ER-negative patients.

Reports also differ on time to first recurrence in ER-positive versus ER-negative tumors. Some studies indicate no significant effects on the DFI between positive and negative ER groups (3, 5, 6, 9). Stewart et al find a prolonged DFI in ER-positive, operable, node-negative patients (7), whereas Howat et al report a statistically significant increase in DFI in ER-positive patients over a median observation period of 24 months, which proved invalid at an extended observation period

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This paper was written when the author was a third-year medical student at Mount Sinai School of Medicine (CUNY). Address reprint requests to Dr. Koenig at Highland General Hospital, 1411 E. 31st St., Oakland, CA 94602.

TABLE 1

Comparison of Studies in Terms of Number of Patients, Length of Follow-Up, and Significant Results

				Results‖			
	No. pts.§	Follow-up (mos)		DFI		Total survival	
Study & date	ER PR	Maximum	Median	ER	PR	ER	PR
This study Nov 1984	207	72	27	+	x	x	x
Review Apr 1984 (2)				x	x	+	x
Howell Mar 1984 (3)	508/486	91	36	–	–	+	+
Mason June 1983 (4)	374	48	33	–	+	+	+
Stewart Oct 1983 (5)	314	60	Not reported	–	–	+	–
Letter May 1984 (6)				x	+	+	+
Stewart Dec 1982 (7)	124/0	78	Not reported	+	x	+	x
Aamdal June 1984 (8)	233/0	Not reported	108	+	x	–	x
Clark Dec 1983 (9)	210/189	57	32	x	+	x	x
Howat May 1983 (10)	175	Not reported	34	–	–	x	x
Andry* 1984 (11)	490/0	103	Not reported	x	x	x	x
Coulson† Sept 1984 (12)	74	36	36	x	x	x	x
Crowe‡ Jan/Feb 1984 (13)	510/0	72	51	+	x	x	x

* No significant correlation of ER content with T category or lymph node invasion was found, but significant correlation between ER content and patient's G grade, menopausal status, and age was found.

† DNA content correlated with estrogen, progesterone, and androgen receptor content.

‡ Presence, but not level, of estrogen receptors is the important prognostic factor.

§ Both estrogen and progesterone receptor values measured.

‖ + = increase; – = decrease; x = no conclusions drawn.

of 34 months (10). Aamdal et al show a decreased DFI in ER-positive stage II patients followed up seven or eight years after mastectomy (8).

The literature on progesterone receptors (PR) is equally perplexing (Table 1). Stewart et al find no difference in survival between patients with PR-positive and PR-negative tumors (5). Gordon and Hubay report that, although PR status is less important than ER status in predicting survival, PR do remain a significant prognostic indicator of total survival (6). Clark et al conclude that PR status is more important than ER for predicting disease-free survival (9). Stewart and co-workers, however, report no significant difference in DFI between patients with PR-positive and PR-negative tumors (5).

It is of great concern whether receptor status by itself is of prognostic significance, or whether the receptor findings are merely a reflection of some other property of the tumor system, since positivity of receptors has been linked to other prognostic factors. Parameters such as tumor differentiation, age of the patient, lymph node involvement, and tumor size must be considered.

Some studies show a highly significant association between the presence or absence of both types of receptor and the histologic grade of the tumor (5, 6). Andry et al actually conclude that, as the degree of differentiation of the tumor increases, the receptor concentration also increases (11). In fact, although older or postmenopausal patients have a significantly higher receptor concentration than their younger counterparts (5, 6, 8, 11, 12), Coulson and co-workers report that patients over 67 years of age with aneuploid tumors had the lowest survival rates (17% after 36 months), compared to 100% survival in patients over 67 years of age with diploid tumors (12).

Mason et al claim that nodal status was the main determinant of DFI, although when patients were grouped by nodal status, receptor levels still indicated subdivisions with significantly longer survival (4). Many studies show no correlation of receptor status to the number of invaded lymph nodes or the size of the primary tumor (3, 10, 11). Although axillary node status and tumor size seem to be prognostically significant in predicting the DFI, several studies have found that these factors have no prognostic power after first relapse (2, 3). Thus, these various factors may be correlated to one another.

The purpose of this study, then, is to examine the effect on disease-free survival of the following five factors: ER level, PR level, extent of axillary lymph node involvement, tumor differentiation, and age of the patient. (NOTE: No data were available on total survival time.)

Materials and Methods

Data on 625 patients at The Mount Sinai Hospital between 1978 and 1984 were collected and compiled to examine these parameters. In 418 cases data were incomplete (that is, at least one of the five factors under study was missing), leaving a total of 207 cases in which both ER and PR levels were measured to be entered into the final analysis.

The following definitions were used: Receptor values of 0–10 fmol/mg of cytosol protein were defined as "receptor negative," whereas values of greater than 10 fmol/mg of cytosol protein were defined as "receptor positive." Patients with positive nodes were defined as those who had at least one histologically proven positive node. Tumor differentiation was assigned a value of 1 if the tumor was "well" or "moderately" differentiated, and a value of 0 if the tumor was "poorly" differentiated as determined from pathologic reports. Patients between 0 and 20 years of age were assigned a year value of 0, between 20 and 40 a value of 1, between 40 and 60 a value of 2, and greater than 60 a value of 3. Disease-free survival was defined as the time between mastectomy and metastasis or, if no metastases were present, the time between mastectomy and death. **Statistical Methods.** A BMDP 2L survival analysis (Cox model) of the data was performed. In addition, correlation coefficients between all five variables were calculated using PROC CORR from the SAS statistical package.

Results

Although nodal status was the most significant determinant of disease-free survival according to the model described above (p = 0.0042), ER level was also highly significant (p = 0.0098). When nodal status was accounted for, ER level became the most significant indicator of DFI. There was no significant correlation between ER level and nodal status (r = 0.01932, Table 2). The next variable to enter the model, after nodes and ER level were accounted for, was age (p = 0.0187). Age was significantly correlated with both ER level and PR level (r = 0.19935 and r = 0.12324, respectively). Finally, when ER level, nodal status, and age were taken into account, tumor differentiation went into the model (p = 0.0619). PR levels did not enter the model, but this could be attributed to the fact that PR level is very highly correlated to ER level (r = 0.70595) and is already in the model.

TABLE 2

Correlation between Estrogen (ER) and Progesterone (PR) Receptor Levels, Nodal Status, Tumor Differentiation (TD), and Age

	ER level	PR level	Nodes	TD	Age
ER level					
r	1.00000	0.70595	0.01932	−0.19222	0.19935
p	0.0000	0.0001	0.6729	0.0001	0.0001
n	527	340	480	388	509
PR level					
r	0.70595	1.00000	0.04581	−0.13326	0.12324
p	0.0001	0.0000	0.4208	0.0314	0.0245
n	340	344	311	261	333
Nodes					
r	0.01932	0.04581	1.00000	0.07008	−0.03955
p	0.6729	0.4208	0.0000	0.1571	0.3589
n	480	311	553	409	540
TD					
r	−0.19222	−0.13326	0.07008	1.00000	−0.11750
p	0.0001	0.0314	0.1571	0.0000	0.0143
n	388	261	409	442	434
Age					
r	0.19935	0.12324	−0.03995	−0.11750	1.00000
p	0.0001	0.0245	0.3589	0.0143	0.0000
n	509	333	540	434	602

r = correlation coefficient; p = p value; n = sample size.

Discussion

The results of this study suggest that, although the extent of axillary lymph node involvement is the most important determinant of disease-free survival, ER status remains highly significant when nodes are accounted for. Tumor differentiation, age, and PR level are all highly correlated with ER level. ER content is of independent prognostic significance and is not merely a reflection of some other property of the tumor system. With regard to PR, no conclusions can be drawn because, in this particular sample, ER was a stronger prognostic indicator of DFI, so that PR did not enter the model. The highly significant positive correlation between ER and PR, however, must be kept in mind (Table 2). The finding that ER status is a prognostic indicator of

DFI is in agreement with the findings of others (7, 8, 13) (Table 1). However, this finding is incompatible with those of Howell, Mason, Stewart, and Howat, although Howat et al did find a trend toward ER significance (3–5, 10).

One possible explanation for these conflicting reports would be the differing definitions of receptor positivity. Not only the definitions, but also the technique of measuring receptor level, vary (13). In addition, even if receptors are present, they may be nonfunctional (2).

Other variables are also subject to various biases. Tumor differentiation, for example, is determined subjectively through morphologic techniques that require a high degree of skill and experience (11).

Any stratification of the data may also potentially change the results. Examples include arbitrary cutoffs of patient age and different subgroupings of tumor differentiation.

A further source of confusion lies in the difficulty of determining the date of metastasis (2). The date of death is generally easy to determine, but the date of recurrence of disease is much more difficult to pinpoint and depends on the method of follow-up.

Adjuvant treatment modalities are another complicating factor. Radiotherapy, chemotherapy, and hormonal manipulations presumably affect prognosis. If receptors are of prognostic significance in their own right, there remains the question of whether increased survival is due to endocrine therapy of these patients. Crowe et al report that women with ER-positive tumors have a greater response to endocrine therapy and a better prognosis compared with women with ER-negative tumors (13). Other researchers state directly that prolongation of survival after mastectomy for patients with receptor-positive tumors is related to the response of metastatic disease to endocrine treatment (2). Furthermore, Howell and co-workers claim that patients not responding to endocrine therapy had identical survival regardless of their tumor receptor status (3). In this sample, women with involved nodes received chemotherapy regardless of their receptor status.

Finally, the question of length of follow-up should be considered. Longer follow-up periods have been shown in some cases to actually reverse results (8). With this in mind, it is difficult to decide what can be confidently used as an acceptable length of time to follow patients up.

Acknowledgments

Thanks to Dr. A. Papatestas and Joan Bratton for their guidance and assistance.

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Final revision submitted February 1987.

Corrections

The following corrections for articles in the January 1988 issue were received too late to be incorporated in the published text.

In Hornykiewicz O, "Neurochemical Pathology and the Etiology of Parkinson's Disease," the author has added reference 11a (Ruberg M, Javoy-Agid E, et al. Dopaminergic and cholinergic lesions in progressive supranuclear palsy. Ann Neurol 1985; 18:523–529), with a citation added on page 12, col. 2, sentence beginning line 15: "Marked striatal dopamine loss has also been found in degenerative brain disorders other than Parkinson's disease that involve parkinsonian symptoms, such as progressive supranuclear palsy (11, 11a). . . ." On page 15, col. 1, line 15 from bottom, sentence should read "Because the striatum . . . critically determined by the highly characteristic [not "variable"] inter- and subregional loss of striatal dopamine." On page 17, col. 1, line 17, sentence should read: "In one of my own studies (48) . . ."; delete citation to reference 46.

In Youdim MBH, "Iron in the Brain," the author notes these changes: page 98, col. 2, line 8, sentence should read: "Although iron-deficient rats were shown to have lower brain iron and diminished behavioral responses to monoamine oxidase inhibitor plus L-dopa D-amphetamine. . . ." The author also adds a new reference, no. 28a (Riederer P, Youdim MBH. J Neurochem 1986; 46:1359–1365), with a citation on page 100, col. 1, first line: ". . . amine oxidase (28, 28a)." and col. 2, line 1, after the word "vivo." Also, an additional citation to reference 9 should appear in the last line of the text, reading ". . . be a long-term process (8, 9)."

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Current Concepts in Treating Elderly Patients: A Decade of Advances

Morris Kleinfeld, Guest Editor

From Kingsbrook Jewish Medical Center, New York

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Ralph Colp Prize

The 1987/88 Ralph Colp Prize for the best surgical paper published in *The Mount Sinai Journal* during the academic year went to Hideki Sakurai, MD, for his article "Carcinoma of the Esophagus: Surgical Treatment with Low Operative Mortality and Low Rate of Anastomotic Leakage" (vol. 54, no. 5). His co-authors were Fouad Lajam, MD, and A. James McElhinney, MD. Dr. Sakurai is with the Department of Surgery at the Veterans Administration Medical Center, Bronx, NY, and is an assistant professor of clinical surgery at the Mount Sinai School of Medicine (CUNY). This and the other *Journal* prizes were presented to the prizewinners at The Mount Sinai School of Medicine graduate awards ceremony on May 17, 1988.

Globus Award

The 1987/88 Globus Prize for the best clinical paper published in this journal during the academic year went to Eldad Melamed, MD, for his paper "Role of the Nigrostriatal Dopaminergic Neurons in Mediating the Effect of Exogenous L-dopa in Parkinson's Disease" (vol. 55, no. 1), which was part of the theme issue "Parkinson's Disease, Alzheimer's Disease, and the Aging Brain." Dr. Melamed holds posts in Israel at the Department of Neurology, Beilinson Medical Center, Petah Tiqva, the Sackler School of Medicine, Tel Aviv University, and the Laboratory of Clinical Neurochemistry, Hadassah University Hospital, Jerusalem. This award honors Joseph H. Globus, founder and first editor of *The Mount Sinai Journal.*

Student Prize

The 1987/88 Student Prize for the best student paper published in this journal has been awarded to Kristi Koenig, MD, for "Prognostic Significance of Hormone Receptors in Breast Cancer" (vol. 55, no. 2), written when the author was a third-year student at the Mount Sinai School of Medicine (CUNY). Dr. Koenig is currently a resident in emergency medicine at Highland General Hospital in Oakland, California.

Appreciation is extended to The Upjohn Company for its partial support of the Tenth Annual Geriatric Seminar at Kingsbrook Jewish Medical Center, Brooklyn, NY, which was held on October 20, 1987, and also for its partial support of this issue publishing articles elaborating the presentations at that seminar.

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Introduction and Overview

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Current Concepts In Treating Elderly Patients: A Decade of Advances

Demographics. Recognition that the proportion of elderly individuals is inceasing at an explosive rate has been for some years a cause of growing concern for the medical fraternity. Statistics predicting that up to 38 million Americans (or 13.6% of our population) will be over 65 by the year 2000 (1) have forced on us the need to develop a better appreciation of what the aging process involves and a clearer understanding of the special characteristics that distinguish this burgeoning segment of the population from younger age groups.

The response to this challenge has been a new emphasis in medical research and education on problems peculiar to or predominant in the geriatric population. The resulting and ongoing new awareness by physicians of the uniqueness of the elderly as a group constitutes a major development which may be expected to improve immeasurably our ability to provide adequate medical care for our older citizens in the coming years.

Physiologic and Psychosocial Factors

It is now well recognized that elderly patients are subject to the influence of certain physiologic, psychological, and sociological factors that do not generally operate in younger individuals.

Psychosocial Frailty. Physicians have become more aware of the psychosocial frailty that often besets the elderly person and of its wide-ranging medical implications. Loneliness, financial problems and the lack of family or supportive friends may significantly impair response to medical treatment or a rehabilitation regimen. The increased utilization of visiting nurses, home assistants, and social workers is a response to this broad problem.

Physiologic Decrements. The physiology of aging is associated with a decrease in reserve which makes the older individual more prone to disease and, once stricken, less capable of recovering the status quo ante. The age-related decline in function is a complex and heterogeneous process, affecting the aging of different individuals, and even different organs within the same individual, at remarkably variable rates of progression. Areas in which physiologic decrements are well characterized include cardiac output, renal function, nerve conduction velocity, perception of pain and thirst, and the integrity of thermoregulatory function and memory. The ratio of fat to hemopoietic tissue in the bone marrow tends to increase with age.

Need for Flexible Application of the "Law of Parsimony." In addition to intrinsic age-related changes, several chronic diseases tend to become prevalent in later life and frequently coexist in the same individual. These include the arthritides, arteriosclerotic cardiac disease, cerebrovascular disease, hypertension, type II diabetes mellitus, and chronic pulmonary disease. We have had to learn that the so-called "law of parsimony" requires flexible adherence when elderly patients are evaluated, because symptomatology may not always stem from a single-system disease. Furthermore, the interaction of the physiologic changes of aging with changes produced by disease may alter function in ill-defined ways, so that it may be difficult to sort out the relative contribution of each.

Sensory Impairments

Loss of taste and smell are common sensory deprivations in the elderly population which can result in malnutrition. Impairment of vision and hearing affects a large proportion of older people. Age-related macular degeneration, cataracts, glaucoma, and diabetic retinopathy are common problems. Fortunately, advances in laser technology have provided several solutions, and laser therapy is now recognized as an effective treatment for early age-related macular degeneration and for certain patients with diabetic retinopathy. It has also proven effective in restoring vision in patients with cataracts. The recent use of intraocular lens implants in the treatment of cataracts is an important advance of this decade. The introduction of screening programs for the early detection and treatment of glaucoma will also prevent further vision loss.

Cardiovascular Disorders

Hypertension Not "Normal" in Older Persons. Ten years ago hypertension in the elderly was widely held to have implications radically more benign than those of hypertension in younger groups. Many specific beliefs in this regard had attained the level of near dogma and were strongly influencing, in an adverse manner, decisions of whether and how to treat. Research during the last decade has, happily, put an end to several of these myths. We now know conclusively from studies conducted in primitive societies that higher blood pressure is not the normal concomitant of aging (2).

We know that the prognosis of hypertension in the elderly is at least as bad as that of similarly elevated pressures in the young (3). We have evidence that treatment of diastolic hypertension in elderly patients has definite beneficial effects in reducing the cardiovascular risk (4) and improving renal function. We have learned that the presence of isolated systolic hypertension is indeed associated with an increased incidence of cardiovascular and cerebrovascular morbidity and mortality. We have, as yet, no evidence that treatment of isolated systolic hypertension does much to reduce that incidence; however, the large-scale Systolic Hypertension in the Elderly Program (SHEP) trial, now in progress, is expected to provide an answer to that question.

New Therapeutic Agents. Along with the advances in our knowledge of the nature of hypertension in the elderly has come a proliferation in the number of drugs available to treat it. These include the majority of beta-blocking agents, the calcium-channel antagonists (verapamil, nifedipine, and diltiazem), and the angiotensin-converting enzyme (ACE) inhibitors (captropril, enalapril and lisinopril), each exerting its specific effects at specific points in the pathophysiologic mechanism and each capable of producing its own set of unwanted side-effects. Provided these agents are used by physicians who have adequate knowledge of their mechanisms and choose the drug most appropriate to the specific clinical situation, their potential effectiveness in reducing mortality and morbidity in the elderly without impairing the quality of life is assured.

Paralleling the advances in antihypertensive medication has been an increase in the number of drugs available to manage cardiovascular disease. Again, we have found that the promise of greater efficacy is accompanied by a greater potential for toxicity.

Hyperkalemia. In his paper, "Heart Failure in the Elderly," Brest underscores the danger of inducing hyperkalemia if potassium-sparing agents, potassium supplements, or both, are incautiously administered to individuals in whom underlying renal impairment is common. ACE inhibitors, by interrupting the synthesis of aldosterone, are also implicated as a potential cause of hyperkalemia in the elderly. Hyperkalemia can cause serious cardiac conduction disturbances or cardiac arrest.

In "Hyperkalemia in an Adult Hospitalized Population," Borra and associates also provide concrete evidence for the need for caution in this regard. Of note is their finding that the increased prevalence of concomitant diseases in the older group puts these patients at higher risk for developing this complication. Of additional note is that the predominant causes of hyperkalemia in the elderly found in this study were iatrogenic conditions, hyporeninemic hypoaldosteronism, and acute renal failure.

Antiarrhythmic Agents. Discussion of medical advances in the treatment of older patients with cardiac disease must include a reference to the expansion in antiarrhythmic agents that has occurred over the last few years. The agents, tocainide, mexiletine, flecanide, encainide, and amiodarone, all of which have received FDA approval, have been shown to be effective in the treatment of patients with ventricular arrhythmias. Amiodarone is the most effective agent available for treating patients with ventricular tachycardia refractory to other antiarrhythmics, but it is also the most toxic of the group.

As first-line therapy the traditional agents, quinidine, procainamide, or disopyramide, warrant trial first. The proarrhythmic effects of flecanide are increased in patients with reduced left ventricular function and history of sustained ventricular tachycardia; thus these drugs should be used with caution in such patients. In all cases, decisions must be tempered by awareness of clinical experiences with the particular antiarrhythmic agent in controlling the rhythmic disturbances in question (5).

Brest points out that available studies do not demonstrate an efficacy of antiarrhythmic agents either in preventing sudden death or in prolonging survival in heart failure (6). Moreover, he cautions that proarrhythmic actions, negative inotropic effects, or systemic toxicity of antiarrhythmics (or all three) may impact adversely on the patient's condition. Although we have learned a great deal about heart failure in the past decade, the syndrome—as Brest intimates—is far more complex than originally envisioned and is growing in magnitude in our population as it ages.

Ischemic Heart Disease. The treatment of ischemic heart disease has also seen revolutionary advances. Management of angina pectoris has benefited from the development of newer beta-adrenergic antagonists which enable the physician to choose individual drugs with particular characteristics in mind (for example, metroprolol for cardioselectivity, pindolol for intrinsic sympathomimetic activity). The development of the calcium-channel antagonists, focusing attention on the supply side of the equation, has provided a new and effective modality for the management of myocardial ischemia. Cardiac catherization with angiography, thrombolytic therapy, and percutaneous coronary angioplasty have been performed with excellent results in elderly patients with acute myocardial infarction (7). However, the incidence of complications increases with age, a fact that should be considered when any of these procedures is contemplated.

Aggressive Management of Postinfarction Patients. Management of patients who have sustained a myocardial infarction has become increasingly aggressive. With the recognition that prolonged inactivity, particularly in elderly patients, often contributes to serious complications of thrombophlebitis, pulmonary embolism, and cardiac and respiratory deconditioning, the emphasis has focused on early, gradual ambulation followed by progressive activities during convalescence. Prolonged inactivity may have devastating psychological effects.

Valvuloplasty. A significant advance in the management of valvular heart disease in the elderly has taken place within the last decade. Catheter balloon valvuloplasty has been employed as a treatment, especially in elderly patients with aortic valvular stenosis who are high-risk candidates for surgery. The results to date are most encouraging (8).

> “Depression is much more common than Alzheimer's disease in elderly persons.”

Psychopharmacology. Stern and Tesar in “Anxiety and the Cardiovascular System” recognize the importance of appropriate identification and management of anxiety and depression in patients with cardiovascular disease. The authors highlight the association of anxiety syndromes and cardiovascular disease, but emphasize the wide spectrum of other causes of anxiety and the need for full investigation of symptoms. They urge an aggressive approach to treatment using psychotherapy and behavioral modification as well as medications. Their concerns are supported by recent studies providing evidence of increased morbidity in cardiac patients suffering from depression (9).

Recent advances in our understanding of brain neurophysiology and its clinical application by psychopharmacologic means have been remarkable, particularly in the treatment of depression, a condition much more common than Alzheimer's disease in the elderly.

In the past decade there has been a proliferation of second-generation antidepressants which are structurally and pharmacologically distinct compounds. Some of these drugs have fewer cardiovascular, anticholinergic, and sedative effects than the tricyclics. However, relatively unique adverse effects are emerging which were rarely seen with the older drugs (maprotiline with its high incidence of seizures, amoxapine with tardive dyskinesia, trazadone with priapism and the potential for exacerbation of ventricular arrhythmias) (10). There appears to be no advantage of these newer drugs in terms of efficacy. Therefore, choosing an antidepressant for an individual is determined largely by the side-effect profile.

Lithium augmentation appears to be a promising treatment for the elderly who are unresponsive to or cannot tolerate other standard therapies (10a). The newer devices for electroconvulsive therapy are now accepted as safe and effective treatment for depression in the elderly (11).

Rheumatologic Disorders

In "Special Rheumatologic Problems of Older People," Plotz gives proper emphasis to the importance of the patient's psychology. The physician who treats the patient with arthritis must—and this might equally apply to many other chronic diseases of old age—maintain a positive and optimistic attitude. Such an attitude can itself be therapeutic, for the patient who believes that the physician has real confidence in the prescribed program will more enthusiastically comply with the regimen.

Plotz reviews the more common rheumatologic disorders of the elderly: polymyalgia rheumatica, giant-cell arteritis, and osteoarthritis. He considers pseudogout, or chondrocalcinosis, to be a subset of osteoarthritis. In his discussion of the latter disease, he refers to several studies indicating that the "wear-and-tear" hypothesis is by itself inadequate and that several other factors besides normal aging may characterize the osteoarthritic population.

He advocates caution in the treatment of older people, particularly in the presence of renal or hepatic impairment. The use of nonsteroidal antiinflammatory drugs requires adequate protection of the gastric mucosa, including the use of simple antacids or H_2-receptor antagonists.

Osteoporosis. Osteoporosis continues to be a problem for many postmenopausal women. Substantial evidence now indicates that estrogen therapy prevents postmenopausal bone loss, and available data strongly suggest that estrogen therapy confers protection against vertebral fractures in both normal women and osteoporotic patients. The use of low-dose estrogen combined with continuous progestin administration appears to be the optimal way to prevent postmenopausal bone loss without causing regular menses, increasing the risk for endometrial cancer, or adversely affecting cholesterol metabolism. The recent introduction of dual photon absorptiometry has provided an improved diagnostic technique for the early diagnosis of osteoporosis; the hip, according to Greenwald, is the preferred site (11a).

Iatrogenic Problems

In keeping with the concerns that have been implicit in the enormous number of new drugs developed in recent years, Hershey, in her paper, "Avoiding Adverse Drug Reactions in the Elderly," provides a comprehensive review of the variety of adverse drug reactions which occur in the older patient and emphasizes the significant incidence of their occurrence in this population. She also proposes appropriate strategies for prevention which, if adhered to, would reduce the incidence of adverse drug reactions.

The subject of drug–food and drug–nutrient interactions has been described and discussed in the past ten years. Roe (12) in her publications on the subject has emphasized that the rapid expansion of this field of knowledge requires practitioners to pursue periodic updates.

Gastrointestinal Tract

Colonoscopy. In a recent review of colon and rectal disease, Salvati (13) states that of all the developments that have taken place in the diagnosis and treatment of colon disease during the past forty years, probably nothing has equalled the dramatic and profound change that the flexible fiberscope (colonoscope) has brought about. This advance has accelerated during the past decade. It has enabled physicians to diagnose colonic polyps and cancer with almost 100% accuracy. The monitoring of inflammatory bowel disease has been vastly facilitated. Colotomy to remove polyps has been virtually eliminated except in the treatment of large sessile lesions. Close follow-up surveillance of patients who previously had polyps has been simplified.

When Should It Be Performed? Spiro, in "Surveillance for Colonic Polyps," is concerned specifically with the issue of when colonoscopy should be performed. He recommends routine colonoscopy only for those with predisposing risk factors. Among such individuals he includes those with first-degree relatives who have had cancer and members of "cancer families"; those who have been found to have an adenoma, particularly over 1 cm in size; and those with such predisposing diseases as inflammatory bowel disease. In addition, he would include regular screening of other patients with irritable bowel syndrome or diverticular disease simply because their chronic symptoms may mask the development of a tumor. However, in an imperfect world, Spiro reflects, he would settle for clinicians investigating thoroughly, with colonoscopy, all their patients with newly developed colonic or rectal bleeding.

The recent introduction of the laser has been most helpful in the management of upper gastrointestinal bleeding.

Urinary Incontinence. Urinary incontinence in the elderly is widespread and is frequently underevaluated and underdiagnosed. Castleden and co-authors have demonstrated that in the elderly incontinent patient, detrusor instability is the most common cystometric finding (39). These workers achieved successful results in many mentally alert patients after treatment by habit retraining supplemented with night-time imipramine therapy. More recently, Resnick and Yalla have reported a variant of detrusor instability in which the bladder is hyperactive, but suffers from decreased contractile function (40). The patient's initial symptom may be urinary retention and the condition may mimic prostatic outlet obstruction. It does not respond to therapy directed at detrusor hyperactivity (bladder suppressants). If the findings of these investigators are replicated in larger studies, this work may have widespread implications for physicians who treat nursing-home patients.

Psychiatric Disorders

Alzheimer's Disease. During the past decade the most prominent advance related to Alzheimer's disease has been the increase in public awareness of its emotional and economic cost. Whereas the psychoses associated with the disease respond to antipsychotic treatment, success in treating the dementia itself has not been achieved even on a limited scale. Preliminary hopes for the drug tetrahydroaminoacridine (THA) in significantly improving responses to cognitive testing and functional abilities (14) have been dampened by more recent reports of unacceptable toxic side effects (15).

Results of inquiry into the etiology of the disease have recently been more promising. The isolation of a genetic defect on chromosome 21 (16) has confirmed an epidemiologic link with Down's syndrome, which shares several clinical and pathologic characteristics with Alzheimer's disease. A second finding that beta-amyloid protein, which is found in extracellular deposits in the brains of patients with Alzheimer's disease, is also coded on the 21st chromosome (17) may mean that a milestone in our understanding of the pathophysiology of Alzheimer's disease has been reached.

Multiinfarct Dementias. In the other great subset of the irreversible dementias, multiinfarct dementia, recent studies indicate that control of such risk factors as hypertension and cigarette smoking may result in an improvement of cognition (18).

Parkinson's Disease. Management strategies for Parkinson's disease continue to rely principally on the use of levodopa for relief of the most troublesome symptoms of the condition. Side effects and loss of efficacy with time continue to be major problems. Amantadine has proven its efficacy in the treatment of Parkinson's disease. The recent introduction of bromocriptine has also been helpful. Perhaps the most hopeful news since levodopa was first utilized are the recent reports of dramatic improvement in symptoms after orthoptic transplantation of adrenal medullary tissue to the periventricular region of the basal ganglia in two young patients (19). The efficacy of the procedure needs to be more fully established before a trial is made in elderly patients with Parkinson's disease.

Infections

Changing patterns in the epidemiology of infectious disease have emerged at both ends of the age spectrum. The advancing average age of the population and the growing use of nursing homes have generated a new population at risk. Nursing-home outbreaks of influenza, tuberculosis (TB) and varicella zoster, a variety of diarrheal diseases, and meningitis have been reported (20).

Tuberculosis. Although rates of TB have shown a dramatic overall decline, the incidence of the disease remains relatively high in the elderly. The recrudescence of old infection, which is known to have a higher incidence in elderly people, cannot explain the increased spread that has been noted to occur in nursing-home settings. Stead has shown that nursing-home patients are at risk also for de novo infection (21). His work and that of others have led to the current recommendation that all nursing-home residents should receive two-step PPD testing at the time of admission in order to identify patients who represent a latent reservoir of TB and are at risk for reactivation TB as well as those who are immunologically naive to TB and susceptible to primary infection. (22).

Influenza. Influenza, usually well tolerated in younger patients, can be a serious illness in the elderly, carrying the potential for life-threatening complications of primary viral or secondary bacterial pneumonia. Excess mortality and morbidity attributable to influenza is extremely high, 90% of excess deaths occurring in persons 65 years of age or older. The institutionalized elderly are at highest risk (23). The widespread use of vaccination has significantly reduced these risks.

A giant stride was made with the introduction of the antiviral agent amantadine, which is also effective in the prophylaxis and treatment of influenza A. Although not a substitute for vaccination, amantadine can be particularly useful as prophylaxis in the case of nonimmunized elderly persons during an outbreak of influenza A, or as therapy, if used within 48 hours of the onset of symptoms (24).

Infections of the Urinary Tract. Urinary tract infections are commonly encountered in elderly patients. Many of the antimicrobial agents that have been available for several years (ampicillin and trimethoprim/sulfamethoxazole) continue to be effective in the eradication of bacteriuria. A recent important addition to the therapeutic armamentarium has been the fluoroquinolone norfloxacin. This new oral agent is active against essentially all urinary tract bacterial pathogens (25). This drug has the power of the parenteral antibiotics. Although not the drug of first choice for urinary tract infections because other antimicrobials are known to be effective against certain pathogens, norfloxacin is quite useful in patients with infections caused by otherwise resistant organisms. The emergence of resistant organisms is infrequent and oral administration is well tolerated.

The issue of whether treatment of asymptomatic bacteriuria, common in elderly patients, is efficacious has continued to be controversial during the past decade. Findings that eradication of bacteriuria is difficult in these patients and that evidence of increased morbidity caused by asymptomatic bacteriuria is lacking indicates that treatment is probably not warranted.

Endocrine Disorders

Morley et al (26) in their recent review of diabetes mellitus in elderly patients have highlighted the fact that diabetes in this population is surprisingly similar to that in younger patients. Older diabetic patients appear to have at least as great a risk of micro- and macro-vascular complications. Good control of the diabetes appears to be important for retarding the development of these complications and improving the quality of life in this population, in which the prevalence is 6.9% in men older than 65 years and 8.9% in women older than 65 in the United States (27). Older patients require more time from their physicians and a greater awareness of the pharmacologic properties of the drugs used to treat them and of potentially hazardous drug–drug interactions.

The recent recommendation of the American Diabetic Association on dietary management of diabetes has improved compliance of the elderly patient. The liberal carbohydrate content (50%–60%) has made the diet more palatable. The new sulfonylureas (glipizide, glyburide), which have a more practical duration of action (18–24 hr) than the old forms and no water-retaining potential, have supplanted the old sulfonylureas in the elderly diabetic.

The recent finding of the efficacy of ACE inhibitors in arresting the progression of diabetic nephropathy will improve the quality of life of the elderly patient with diabetes. (28).

Renal Disorders

Dialysis. During the past decade, dialysis has been extended to include older patients with end-stage renal disease, so that the elderly now constitute the largest number of new recipients of this therapy. In the annual report dated 1986 by the Network No. 25 Inc., New York State, the incidence of dialyses therapy in the group aged 70–79 years increased significantly, from 380 patients in 1985 to 467 in 1986. In elderly persons who do not have diabetes, cardiac disease, malignancy, pulmonary disease, or uncontrolled hypertension, the efficacy of dialysis is quite satisfactory (29), despite the higher mortality among elderly persons as a whole.

New Techniques. Continuous ambulatory peritoneal dialysis has permitted elderly patients with cardiovascular instability to be dialyzed at home without serious risk.

The recent introduction of the technique of continuous arteriovenous hemofiltration has been beneficial in elderly patients with acute renal failure. The technique eliminates the elaborate extracorporeal circuitry used for end-stage renal disease (30). This method offers many advantages over conventional hemodialysis, including control of fluid balance, acid-base hemostasis, and allowing parenteral nutrition.

Renovascular disease in the elderly is due principally to atherosclerotic obstruction of the renal arteries. The use of percutaneous balloon angioplasty has helped to improve renal function and to simultaneously reduce the associated elevated blood pressure. The technique has been expanded to include dilatation of branches of the renal arteries.

Anemia. The success of recombinant DNA technology in producing human erythropoietin for treatment of anemia of chronic renal disease has opened the door for effective therapy of this hitherto vexing problem (31).

Pulmonary Disorders

Chronic obstructive pulmonary disease (COPD) continues to be a major challenge. The increasing prevalence with aging is largely attributable to the etiologic role of long-term cigarette smoking in susceptible individuals; duration of smoking is likely to be greater in elderly smokers. In addition, we have learned much about the contributing age-related structural changes in the respiratory system, which include decrease in lung elasticity, increase in chest-wall stiffness, and decline in respiratory muscle strength. The cumulative result is a gradual, but progressive, reduction in forced vital capacity, expiratory flow rates, diffusing capacity, and gas exchange (32).

A pathogenetic mechanism for emphysema associated with inherited alpha-antiprotease deficiency conditions has recently been elucidated (33). What is involved is an insidious destruction of alveoli and small airways by proteolytic and oxidative activity. Similar mechanisms may underlie the pathogenesis of adult respiratory distress syndrome (34) and lung cancer. Such discoveries have initiated research efforts aimed at developing effective therapy. Replacement of antiproteases in individuals suffering from deficiency-related emphysema has been attempted, using an enzyme produced by recombinant DNA technology (35). The same enzyme has also been used effectively to ameliorate emphysema produced in animals by human elastase (36). Much remains to be discovered in this promising new area.

Lung Cancer. In lung cancer patients with malignant air flow obstruction, the development of the YAG laser has made possible the opening of obstructed bronchi (37). Although the survival rate of such patients remains dismal, the procedure is a valuable palliative that may buy time for the patient and the family to come to terms with the inevitable.

For the present, with respect to both COPD and lung cancer, the proper emphasis continues to be on prevention. Although we have much still to do, a great deal has been achieved. Ten years ago the idea of a smoke-free society was barely conceivable. Today, it is a realistic goal.

The development of new technologies has facilitated the rehabilitation of pulmonary patients both in hospital and, by the use of systems delivering oxygen to ambulatory persons, in the home setting. A superb study carried out by the Division of Lung Diseases of the National Heart, Lung, and Blood Institute has convincingly demonstrated that, in hypoxemic chronic obstructive lung disease, continuous low-flow oxygen therapy is associated with lower mortality when compared to nocturnal oxygen therapy (38).

A Brief Precis: Other Technologic Advances

The task of attempting to provide an overview of some of the major developments which have molded and expanded the practice of geriatric medicine over the last decade is, indeed, a daunting one. Limitations of space impose severe restrictions both on the number of topics that can be discussed and on the degree of detail that each topic can be allotted. Only a brief mention has been made of some of the technological advances that have changed not just the geriatric field, but medicine as a whole. The decade has seen the further development of computer tomography and the introduction of the newer technologies of magnetic resonance imaging (MRI) and positron emission tomography (PET), which continue to be refined as designs are improved and new applications constantly investigated. New clinical applications of ultrasonography continue to be discovered, including endorectal ultrasonography for the early detection of cancer of the prostate. Doppler ultrasonography is being used successfully in the evaluation of cardiac carotid artery lesions and is finding a wider application in detecting obstructions in intracranial and intraabdominal vessels. Laser angioplasty is showing promise in the opening of occluded peripheral arteries. Shock-wave lithotripsy has proven invaluable in the treatment of renal calculi and is recently proving to be effective in the treatment of gallstones. Venous valve surgery for deep venous insufficiency in the elderly has come into more frequent use and has proven to be beneficial. The science of molecular biology is being applied with increasingly gratifying results in understanding cancers and in developing therapeutic products for them. Approaches to the management of certain cancers are changing as our knowledge grows (for example, the use of alpha-interferon in the treatment of hairy-cell leukemia). The list is inexhaustible and any attempt to do justice to the new technology would require another paper of considerable length.

It is my modest intention here, by highlighting certain relevant advances and alluding briefly to others, to convey to the reader something of my own sense of admiration at what has been and is continuing to be achieved. I am pleased to take this opportunity to thank the authors of this symposium for their contributions to that achievement.

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Heart Failure in the Elderly

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Heart failure is a major cause of morbidity and mortality in the elderly. The prevalence of heart failure increases exponentially with age and the prognosis is poor, less than half the patients surviving five years after the diagnosis is established (1). In comparison with younger patients, there is a greater tendency to overlook the etiology of heart failure in the aged and, instead, simply to treat the manifestations. Moreover, coexisting systemic (pulmonary, renal, nutritional, and other) disorders are more apt to confound the recognition of heart failure and thus delay its treatment. Yet the need for early recognition and prompt comprehensive management is mandatory if prognosis is to be optimized. The principles of diagnosis and management of heart failure in the elderly are not remarkably different from those in the young; most importantly, the clinical approach must be systematic, and attention to detail should be impeccable.

Clinical Considerations

Heart failure does not occur de novo; the underlying heart disease must be identified, and precipitating and aggravating factors recognized and reversed.

Etiology. With regard to etiology, older as well as younger adults are most likely to suffer from ischemic or hypertensive heart disease. However, valvular disease is not uncommon in older individuals, particularly calcific aortic stenosis; and the elderly are prone also to suffer from mitral regurgitation secondary to coronary artery disease and its complications, or mitral anular calcification (which occurs predominantly in the elderly), or mitral valve prolapse secondary to myxomatous degeneration (2). Ruptured chordae tendineae may occur in association with either of the latter two conditions, with infective endocarditis or as an isolated disorder.

Cardiomyopathy is less common in the aged but is certainly not unusual (3). Alcoholism, diabetes mellitus, and nutritional disorder should be considered in the differential diagnosis of congestive cardiomyopathy, and amyloidosis in cases of restrictive cardiomyopathy. Hypertrophic cardiomyopathy too is often either unrecognized for long periods or else misdiagnosed, because of the mistaken impression that this disorder is rare in the elderly.

Other diagnostic pitfalls in the aged include failure to recognize (a) the potential long-lived natural history of certain congenital cardiac anomalies such as atrial septal defect, (b) the intermittent nature of serious cardiac conduction disturbances, for example severe sinus bradyarrhythmia associated with sick sinus node syndrome, (c) the hemodynamic default associated with loss of atrial contribution to ventricular filling (as encountered with atrial fibrillation) or loss of atrioventricular synchrony (as occurs with complete heart block or asynchronous pacing), or (d) the overshadowing of heart failure manifestations by concomitant systemic disorders, for instance obstructive lung disease, renal or thyroid disorders. Infective endocarditis also fits into the latter category; that is, the condition is by no means rare in the elderly, yet its systemic or constitutional manifestations may cloud the diagnosis and thus delay treatment to the point at which cure becomes unduly difficult, if not impossible.

Overall, successful management of heart failure is dependent upon the recognition of the underlying cardiac disorder; empirical treatment alone may be ineffective.

Diagnosis. Regarding diagnosis, the history and physical examination are indispensables, in

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the elderly as in the young, in the recognition of both the heart failure and the underlying cardiac disorder. Likewise, chest x-ray, ECG, echocardiogram, radionuclide studies, and Holter monitoring are informative in patients of all ages. Age per se also is no bar to exercise testing, which can be employed in the diagnosis of ischemic heart disease, in the quantitation of exercise capacity, and in the monitoring of response to anticongestive therapy (4). Moreover, one should not hesitate solely because of the patient's age to recommend invasive tests such as cardiac catheterization or electrophysiologic study, whenever it seems likely that the information to be gained cannot be achieved by other means, or when the complementary information provided by these studies is needed to make crucial decisions regarding management, for example, coronary bypass or angioplasty, or valvular surgery.

Treatment and Prevention. Heart failure sometimes seems to occur as a natural progression of the underlying cardiac condition. More often, with careful attention to detail, one can recognize the triggering event that precipitated the cardiac decompensation. Myocardial infarction, cardiac dysrhythmia, and infection are especially common initiating factors. A host of other organic as well as environmental factors also may be responsible; for example, acute valvular regurgitation, coronary insufficiency, prostatic obstruction, drugs that promote sodium retention such as nonsteroidal antiinflammatory agents, drugs that depress myocardial function such as beta blockers, undue physical workload, alcohol abuse, or dietary indiscretion including salt or fluid overload.

Recognition of the precipitating event may be crucial both to treatment and, equally or more importantly, to the prevention of recurrent cardiac decompensation. In addition to consideration of initiating factors, one should also be alert to the coexistence of any aggravating factors that may be contributing to the cardiac failure; for example, coexisting anemia, nutritional deficiency, or thyroid or pulmonary dysfunction can contribute to the development of refractory heart failure, unless recognized and treated concomitantly.

Aids to Compliance. The issue of patient compliance (with regard to nutrition, smoking, alcohol, exercise, drug therapy, and so on) is neither more nor less important in any adult age group. However, aging does present some particular problems. For example, declining cognitive function or visual impairment may call for special written instructions or for social service consultations in order to achieve the desired goals. Elderly patients must understand their needs and physicians must help them find practical solutions to medical recommendations; otherwise, conditions such as heart failure are apt either to be incompletely treated or else to become refractory, simply because the patient is unable, rather than unwilling, to comply with dietary, medication, or other recommendations made by their physicians.

Therapeutic Considerations

Primary goals in the management of heart failure include (a) recognition and specific treatment (whenever possible) of the underlying cardiac disorder, and (b) correction of any contributing extracardiac conditions (such as infection, hypertension, anemia, alcohol excess, inadequate nutrition, thyroid or renal dysfunction, electrolyte imbalance, or pulmonary disorder). Concomitantly, optimum management requires attention to each of the physiologic factors governing cardiac performance: myocardial contractility, heart rate and rhythm, preload (venous return), and afterload (blood pressure).

Diuretic drugs induce a reduction in the blood volume (preload), and the concomitant decrease in intracardiac volume and pressure may result in accompanying improvement in cardiac performance. Diuretic drug therapy is sometimes effective alone, without other therapeutic interventions, in the control of cardiac failure. However, it is physiologically more rational to employ diuretic drugs in conjunction with other appropriate therapeutic measures in the overall management of this disorder.

Reduction in the preload is enhanced not only by diuretic drug therapy but also by sodium and fluid retention and by venodilator drugs (such as nitrates). Myocardial contractility may be improved directly by inotropic agents, such as digitalis. Additionally, certain cardiac dysrhythmias (both tachyarrhythmias and bradyarrhythmias) may seriously compromise cardiac function, and therefore it follows that such dysrhythmias should be treated concomitantly. Moreover, suppression of complex ventricular ectopy has been promoted not only as a means of improving ventricular function, but also as a treatment that prolongs survival. Arterial dilators (such as converting enzyme inhibitors and hydralazine) may exhibit beneficial effects by decreasing impedance to left ventricular emptying. Finally, in some instances, heart failure cannot be controlled without cardiac surgical or other mechanical interventions. Successful management of cardiac failure requires systematic attention to each of these therapeutic interventions.

Diuretic Drugs. Diuresis not only obviates the secondary manifestations of heart failure (pulmonary rales, hepatic congestion, and peripheral edema), but also increases cardiac efficiency by decreasing heart size. The thiazides, introduced thirty years ago, were the first potent, orally effective diuretic agents. Unquestionably, these drugs revolutionized the treatment of congestive failure. Chlorothiazide, the first thiazide, was followed by a host of related sulfonamide compounds. Although the various thiazides and thiazide-type drugs differ with regard to milligram potency and duration of action, their pharmacodynamic activity, side effects, and clinical aplications are similar (5).

The thiazides and related drugs act at the distal cortical diluting segment of the nephron. They inhibit sodium reabsorption and, like the loop diuretics, interfere with the generation of free water. However, because of the lesser absorption of sodium that ordinarily occurs in the distal nephron, these drugs exhibit less natriuretic potency than the loop diuretics, which act more proximally. Conversely, the thiazides and their congeners are more potent than the potassium-sparing drugs that act even more distally in the nephron.

The thiazides and the thiazide-type drugs are the diuretic agents of choice in the management of cardiac edema of mild to moderate severity, except in the presence of significant renal functional impairment. These drugs are relatively ineffective when used alone in patients with renal insufficiency. In this regard, metolazone is the one exception in that it may induce diuresis even in patients with glomerular filtration rates below 20 ml/min. The effectiveness of metolazone in this situation is probably due to its more powerful inhibitory effects in the proximal tubules, in comparison with related compounds.

The loop diuretics interfere with sodium chloride reabsorption in the ascending limb of the loop of Henle. The three loop diuretics that are commercially available (furosemide, ethacrynic acid, and bumetanide) are chemcially different, but their pharmacodynamic effects are remarkably similar. In contrast to the thiazides, the loop diuretics exhibit a much steeper dose-response curve. Moreover, these drugs may be remarkably effective even when renal function is substantially impaired. Their ability to reduce renal vascular resistance and to readjust blood flow within the renal parenchyma (from the inner cortex and outer medulla to the outer cortical region) apparently accounts, at least in part, for their beneficial activity under conditions of reduced renal function.

Because of their marked potency, the loop diuretics are preferred in patients with cardiac edema that is refractory to treatment with less potent diuretic agents. Also, they may be uniquely useful in the presence of coexistent renal failure, whether the heart failure is mild or severe. Moreover, because of their rapid onset of activity and great diuretic potency, these diuretics administered parenterally have become the diuretics of choice in the treatment of acute pulmonary edema.

The potassium-sparing diuretics (amiloride, triamterene, and spironolactone) block potassium-sodium exchange in the distal portions of the nephron (distal convoluted tubule and early collecting duct), thereby conserving potassium while promoting sodium excretion. Because they act distally after most of the sodium has been reabsorbed, these agents exhibit only mild diuretic action when used alone. In order to achieve substantial diuresis, these drugs must be used in combination with other, more potent diuretic agents. When potassium-sparing drugs are administered with thiazides or loop diuretics, the diuretic response to the latter agents is substantially enhanced, probably because the effects of secondary hyperaldosteronism are largely blocked. Consequently, combined therapy not only reduces potassium excretion and minimizes alkalosis, but it is also quite effective in mobilizing refractory edema fluid.

Diuretics in Elderly Patients. In contrast to younger adults, elderly patients more commonly exhibit underlying renal impairment. Thus, they are more likely to exhibit dangerous hyperkalemia when potassium-sparing agents, potassium supplements, or both are administered (6). Likewise, converting enzyme inhibitors and salt substitutes increase the likelihood of hyperkalemia. Similarly, because glucose tolerance is often impaired in the elderly, they are apt to exhibit thiazide or loop-diuretic-induced hyperglycemia. Disorders of urination also are common in the elderly, and, therefore, urinary incontinence or retention are encountered not infrequently in aged patients treated with potent diuretics.

Digitalis. Digitalis is the prototypal inotropic agent and a perennial mainstay in the treatment of chronic heart failure. Both clinical and hemodynamic improvement is observed in some patients with cardiac failure, but others do not exhibit any beneficial effects. Moreover, concerns have been raised that prolonged inotropic stimulation might adversely affect survival in patients with severe chronic heart failure (7).

A good deal of the confusion (and therefore the controversy) about the usefulness of digitalis in the treatment of heart failure seems to stem from the tendency, at least in some quarters, to generalize about the role of digitalis, without taking into full account the underlying type of heart disease and the nature of the cardiac dysfunction. In this regard, the chronic heart failure patient whose initial symptoms are cardiac dilation and systolic dysfunction is clearly quite different from the patient with normal heart size and diastolic dysfunction. Thus, the patient with unremitting heart failure due to chronic ischemic cardiomyopathy is much different clinically from the patient who exhibits recurrent heart failure due to acute attacks of coronary insufficiency. Each of these patients could be labeled as having heart failure due to coronary disease, but the underlying mechanisms, the prognosis, and the response to treatment obviously are quite different.

Hence it is understandable why confusion abounds about the therapeutic role of digitalis and other inotropes in heart failure. It is likely that neither the confusion nor the controversy will abate in the near future. Nonetheless it is probable that digitalis will continue to be widely employed, at least until some more definitive studies or more useful inotropes are forthcoming.

Digitalis in Elderly Patients. Gastrointestinal symptoms and ventricular arrhythmias are the most common untoward reactions encountered with digitalis, both in younger and in older patients. However, the elderly are particularly prone to manifest neurologic symptoms (altered visual perception, muscle weakness, undue fatigue), psychiatric problems (agitation, drowsiness, hallucinations), or anorexia and weight loss (6). Also bear in mind that the elderly are likely to exhibit coexistent renal functional impairment, which calls for reduction in digoxin dosage. It must be remembered, too, that digoxin dosage varies with body size, smaller patients requiring lesser dosage. Monitoring of serum digoxin dosage may be needed more often in elderly (as compared with young) patients treated for chronic heart failure, especially those in sinus rhythm.

Vasodilator Drugs. Significant anticongestive effects can be achieved both by venous and by arterial dilation. Nitrates exhibit predominant venodilation; therefore, like the diuretics, these drugs are used in heart failure primarily to reduce the associated congestive effects, particularly pulmonary congestion. Whereas nitrates affect the preload especially, arterial dilators, such as hydralazine, primarily affect (reduce) the afterload, that is, the systemic vascular resistance. Thus, arterial dilators serve mainly to unload the left ventricle, which in turn enhances left ventricular emptying and increases the cardiac output. Combination venous and arterial dilator therapy can yield both immediate and long-term therapeutic benefits. Indeed, the Veterans Administration Vasodilator Heart Failure Trial demonstrated extended survival in heart-failure patients treated with the combination of isosorbide dinitrate and hydralazine (8).

Heart failure invokes the activation of several neurohumoral systems, particularly the sympathetic nervous and the renin-angiotensin-aldosterone systems (9). The elaboration of vasopressors—catecholamines and angiotensin II—has mixed physiologic effects. On the one hand, these two vasoconstrictors provide vascular support by sustaining the systemic blood pressure, but they act also to adversely affect ventricular function, enhance ventricular ectopy, and promote edema formation. Beta blockers have been employed successfully in some cases of dilated cardiomyopathy to overcome catecholamine-induced tachycardia, thereby enhancing stroke volume and cardiac output. However, the negative inotropic effects of beta blockade often overcome the potential benefits, and, therefore, beta blockers are best avoided in heart failure except in highly selected cases in which close patient monitoring (preferably in the hospital initially) can be undertaken.

In contrast to beta blockade, the use of angiotensin-converting-enzyme inhibitors in heart failure has been attended by greater therapeutic benefits and fewer adverse effects. Moreover, there is a growing clinical consensus that converting-enzyme inhibitors are the vasodilator agents of choice for most patients selected for afterload reduction. Although it has been suggested that responsiveness of the renin-angiotensin system diminishes with age, available studies indicate that this system is intact in the elderly (10). These findings imply that converting-enzyme inhibitors should be as effective in elderly as in younger patients with heart failure, and clinical experiences support this contention.

A recent study compared the effects of captopril treatment with those of digoxin treatment during maintenance diuretic therapy in patients with mild to moderate heart failure (11). Significant improvements in exercise tolerance and functional class compared with a placebo group were found in the captopril-treated but not in the digoxin-treated patients. However, digoxin treatment increased ejection fraction more than captopril therapy and placebo. It was concluded from this study that captopril is an effective alternative to digoxin in patients with mild to moderate heart failure.

Studies investigating drug treatment of heart failure often are aimed primarily at determining which is the best therapy—converting enzyme inhibitors, other vasodilators, digitalis, or diuretics. However, there is no particular reason why heart failure should be treated by a single therapeutic intervention; it makes greater clinical sense to treat concomitantly all clinical conditions and all physiologic factors governing cardiac performance, thereby optimizing the management of cardiac failure.

Cardiac Arrhythmias. Chronic heart failure is associated with a high incidence of complex ventricular arrhythmias and sudden death (12). There are multiple mechanisms in heart failure patients that could account for ventricular ectopy, including increased levels of circulating neurohormones, focal areas of electrical instability in the myocardium (related to scarring), electrolyte abnormalities, and myocardial ischemia. In addition, detrimental effects of cardiorenal drugs, particularly inotropes and diuretics, may contribute to ventricular dysrhythmias. In general, the greater the depression of ventricular function, the higher the incidence of ventricular ectopy and sudden death (13).

Because of the association of ventricular arrhythmias and sudden death in heart failure, it is tempting to employ antiarrhythmic drug therapy in an attempt to enhance survival. However, available studies do not provide support for the effectiveness of antiarrhythmic agents either in preventing sudden death or in prolonging survival in heart failure (14). Moreover, proarrhythmic actions, negative inotropic effects, and the systemic toxicity of antiarrhythmics may each have an adverse impact on the patient's condition.

Ventricular ectopy tends to lessen when heart failure improves. In some studies, treatment with specific anticongestive agents, for example captopril, has been associated with a significant reduction in the frequency of ventricular arrhythmias (15). Based on present knowledge, however, the maximal treatment of ventricular ectopy can be achieved best by optimizing cardiac function and by decreasing the adverse byproducts of heart failure, for example by restoring electrolyte balance and by decreasing the concentration of circulating neurohormones, whenever feasible.

Cardiac Surgery. Not uncommonly, heart failure is due fundamentally to cardiac conditions that are mechanical: valvular stenosis or regurgitation, intracardiac shunt, or myocardial aneurysm. Reversal or mitigation of cardiac failure in such instances often cannot be achieved unless the underlying disorder is corrected or palliated surgically. Other disorders, such as coronary heart disease, usually can be treated adequately by medical means but, in some instances, concomitant surgery is needed to control ischemic or congestive manifestations.

Elderly patients requiring cardiac surgery are more likely than young patients to have concomitant noncardiac conditions that can complicate surgical intervention—systemic disorders such as diabetes mellitus, obstructive lung disease, renal failure, peripheral vascular disease, carotid artery disease, nutritional deficiency. Moreover, age beyond 65 years has been shown to be an independent predictor of mortality in some surgical series (15). Nonetheless, there are ample studies indicating that cardiac surgery can be undertaken with reasonable expectations in carefully selected patients (16). Thus, the surgical option should be offered to patients, regardless of age, whenever surgery is considered a viable therapeutic alternative.

Summary

Given our aging society, we can expect to encounter increasing numbers of elderly patients with heart disease complicated by heart failure. The keys to optimal management of cardiac failure include early detection and comprehensive attention to all anatomic factors and physiologic variables affecting cardiac performance. With a systematic approach, reduced disability and prolonged survival can be anticipated.

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Hyperkalemia in an Adult Hospitalized Population

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Abstract

Hyperkalemia poses serious cardiac conduction disturbances which can lead to ventricular fibrillation or standstill. We conducted a prospective study of the causes of hyperkalemia ($K^+ \geqslant 5.5$ mEq/L) in an adult hospitalized population of 71 patients. The predominant causes of hyperkalemia in the 55 patients older than 60 years were iatrogenic (43.6%), hyporeninemic hypoaldosteronism (21.8%), and acute renal failure (14.5%), whereas in the 16 patients aged 60 years or less, the predominant etiology was end-stage renal disease (creatinine clearance <5 ml/min) (68.7%).

We attribute the high incidence of iatrogenic causes in those older than 60 years to the higher number of prescribed drugs taken by the older population, and especially the use of potassium supplements and potassium-sparing diuretics in the presence of moderate renal insufficiency (creatinine clearance ≅20 ml/min). The majority of patients with end-stage renal disease showed adequate hormonal response to hyperkalemia. High aldosterone secretion maintains K^+ hemostasis. The greater predisposition to hyperkalemia in the elderly group (>60 years) was due to the increased prevalence of concomitant diseases. In 15 of the 71 patients we studied, the cause of hyperkalemia was multifactorial.

We conclude that close monitoring of serum K^+ is required, particularly in elderly patients and in those patients receiving intravenous hyperalimentation and on maintenance hemodialysis.

Hyperkalemia can produce serious cardiac conduction disturbances or cardiac standstill. Shemer et al (1) in a recent study observed hyperkalemia ($K^+ \geqslant 5.3$ mEq/L) to be present in 10% of all medical ward admissions during a two-month period. The causes of hyperkalemia were multiple. They found that aging was a relative risk factor for developing hyperkalemia.

The purposes of this study were to (a) determine the incidence of hyperkalemia ($K^+ > 5.5$ mEq/L) in a general hospitalized adult population over a defined period (10 weeks), (b) ascertain if the etiologies of the hyperkalemia in the individuals 60 years or less and those older than 60 years, varied significantly, and (c) ascertain if the factor of aging was a predisposing cause for hyperkalemia in this population.

Methods and Procedures

The study, a prospective design, was carried out during a 10-week period in 1985. A total of 1,775 patients (Table 1) were admitted to the adult medical and surgical wards during the period of observation. Of the 1,775, 98 (5.52%) had hyperkalemia at the time of admission or developed hyperkalemia during their hospitalization.

Seventy-one of the 98 patients completed the protocol (77.17%). The other 27 were excluded from the study because data were incomplete as a result of the patient's early discharge or death. The protocol included medications administered to the patient and amount of sodium intake in

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TABLE 1

Correlation of Incidence of Risk of Hyperkalemia by Age and Sex in 1,775 Patients

Population		Hyperkalemics	Incidence	*P*
Total	1775	98	5.52%	
By Sex				
Males	731	31	4.24%	=.06
Females	1044	67	6.41%	
By Age				
>60 years	1151	78	6.33%	<.01
$\leqq$60 years	624	20	3.22%	

the diet. The laboratory tests included serum electrolytes (Na^+, K^+, Cl^-, HCO^-_3), blood urea nitrogen, creatinine, glucose, serum lipids, complete blood and platelet counts. These determinations were made using standard autoanalyzer techniques. Arterial blood gases, serum and urine osmolarities, urine pH, and 24-h urine Na^+ and K^+ were also measured. The endocrine tests included plasma cortisol at 8:00 AM (normal 138–691 nmol/L); plasma aldosterone with the patient in supine position (normal 50–250 pmol/L) and after stimulation (normal 2–4-fold rise over baseline level); plasma renin with the patient supine (normal 0.15–2.3 ng/ml per hour) and after administering 40 mg furosemide intravenously and maintaining the patient in upright position. All radioimmunoassays were performed by either Roche Biomedical Laboratories, Roche Drive, Raritan, NJ or Upjohn Laboratories, King of Prussia, Pa. Electrocardiograms were taken on each patient.

TABLE 3

Iatrogenic Causes of Hyperkalemia in 25 Patients

Cause	No. of Patients
Nonsteroidal antiinflammatory agents (Indomethacin)*	3
K^+ supplement in patients with moderate renal failure†	12
K^+ supplement simultaneously with K^+-sparing diuretics	4
K^+-sparing diuretics in presence of moderate renal failure†	3
Angiotensin converting enzyme inhibitors (captopril)	2
Beta blockers (propranolol)	1
Total	25

* In patients with moderate renal failure.

† Clearance of creatinine $\cong$ 20 ml/min.

All serum K^+ determinations obtained by the laboratory during the 10-week period were reviewed for elevated serum K^+ levels, defined as $K^+ > 5.5$ mEq/L. Whenever an abnormal serum K^+ level was found, a second sample from the same patient was obtained. If the hyperkalemia persisted, the patient was considered for the study. Abnormal values attributed to hemolysis or laboratory error were excluded from the study.

The diagnosis of hyporeninemic hypoaldosteronism was made when the patient had normal glucocortcoid function, mild to moderate renal insufficiency (creatinine clearance $\cong$ 20 ml/minute), low or low normal baseline plasma aldosterone level with subnormal increase following volume contraction. Plasma renin was low normal at baseline and after stimulation. The criteria for end-stage renal disease was a clearance of creatinine of less than 5 ml/min.

Results

The mean age of the 1,775 hospitalized population was 67.4 years (range, 18 to 103 years).

TABLE 2

Cause of Hyperkalemia Correlated with Age in 71 Patients

	Total		$\leqq$60 Years		>60 Years	
Causes	No.	(%)	No.	(%)	No.	(%)
Iatrogenic	25	(35.21)	1	(6.25)	24	(43.63)
ESRD*	16	(22.54)	11	(68.75)	5	(9.09)
Hyporeninemic hypoaldosteronism	14	(19.72)	2	(12.50)	12	(21.81)
Acute renal failure	8	(11.27)	0	(0.00)	8	(14.54)
Increased tonicity†	4	(5.63)	2	(12.50)	2	(3.63)
Dehydration‡	3	(4.22)	0	(0.00)	3	(5.45)
Spurious§	1	(1.41)	0	(0.00)	1	(1.81)
Total	71	(100)	16	(100)	55	(100)

* End-stage renal disease.

† Three patients received intravenous hyperalimentation and one patient had uncontrolled diabetes mellitus.

‡ Determined clinically.

§ Patient had elevated WBCs and platelets secondary to myeloproliferative disorder.

There were 1,151 patients older than 60 years and 624 patients aged 60 years or less (Table 1).

The 98 hyperkalemic patients had a mean age of 71.09 years (range, 20 to 99 years). Seventy-eight were older than 60 years and 20 patients were aged 60 years or less. The difference in the incidence of hyperkalemia by sex (Table 1), using chi square with and without correction of continuity, was not statistically significant ($P = .06$).

The difference in the incidence of hyperkalemia by age was statistically significant ($p < .01$), using the same statistical methodology.

Cause of hyperkalemia in 71 patients was correlated with age (Table 2). In the 55 patients older than 60, iatrogenic causes (Table 3) were predominant (43.6%), whereas the most common cause of hyperkalemia among the 16 patients aged 60 years or less was end-stage kidney disease (68.7%).

The plasma aldosterone level was correlated with serum K^+ (Fig.) in 16 patients with end-stage kidney disease (11 aged 60 or less and 5 older than 60 years). With the exception of 3 patients, all the others showed adequate hormonal response to hyperkalemia, indicating that high aldosterone secretion rates play a role in maintaining K^+ homeostasis in this group of patients.

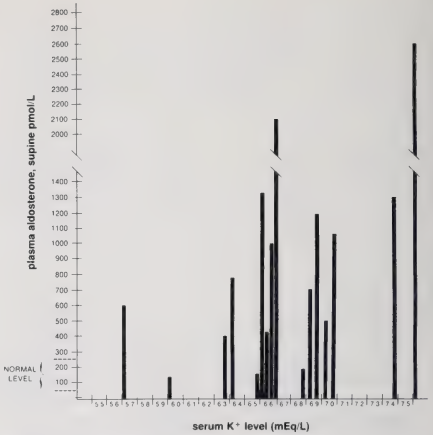

Fig. Plasma aldosterone levels correlated with serum K+ in 16 patients in dialysis.

Discussion

Shemer et al. (1) reported that the incidence of hyperkalemia among 1,714 medical ward admissions was 10%. The patients in their study were similarly divided into two groups, those 60 years or less and those older than 60 years. Shemer et al. excluded patients who were on maintenance dialysis, whereas our study did not exclude this group of patients. In spite of our inclusion of these patients, the overall incidence of hyperkalemia was 5.52%, in contrast to the 10% found by Shermer et al. (1). Their higher incidence of hyperkalemia can be attributed to a large percentage of their patients (55%) having K^+ levels between 5.3 and 5.4 mEq/L. They also observed a threefold increase in the overall incidence of hyperkalemia in those aged over 60 years of age. Our data are consistent with theirs with regard to age (Table 1). Another similarity between the two studies was the absence of a statistically significant difference in sex incidence.

The predominant causes of hyperkalemia in the 55 patients older than 60 years who completed the study were iatrogenic (43.6%), hyporeninemic hypoaldosteronism (21.8%), and acute renal failure (14.5%), whereas in the 16 patients who were 60 years or less, the predominant etiology was end-stage renal disease (68.7%).

The high incidence of iatrogenic causes in those older than 60 years is attributed to several factors, the first being the increased use of drugs prescribed for the older population, especially the use of K^+ supplements and K^+-sparing diuretics in the presence of moderate renal insufficiency (creatinine clearance approximately 20 mL/min) (2–6). In addition, the older patients are more likely to be receiving nonsteroidal antiinflammatory agents (7, 8) for arthritis, and angiotensin-converting enzyme inhibitors for the treatment of hypertension (9).

Hyperkalemia is prominent in the syndrome of hyporeninemic hypoaldosteronism. The syndrome occurs frequently in those who are diabetic and have moderate renal insufficiency (10–13), and these factors were found in our study, predominantly in those older than 60 years. For example, 8 out of 12 patients with hyporeninemic hypoaldosteronism were diabetic and had moderate renal failure. Many of these patients were admitted to the hospital with serum K^+ of 5.0 to 5.4 mEq/L and became frankly hyperkalemic ($K^+ > 5.5$ mEq/L) whenever they were given a low sodium diet, an outcome previously observed by Pelleya, Oster, and Perez (11). The low sodium intake upset their K^+ balance and made them more severely hyperkalemic. The primary cause of the hyperkalemia was linked to hyporeninemic hypoaldosteronism, and was therefore included under this category rather than in the category of iatrogenic hyperkalemia.

In 15 individuals, the cause of hyperkalemia was multifactorial. In this study, the primary cause of elevated K^+ was used to classify patients. For example, a patient with acute renal failure induced by aminoglycosides who was taking K^+ supplements was classified in the "acute renal failure" group.

End-stage renal disease was the most frequent cause of hyperkalemia in those 60 years or less in our study. Thirteen of the 16 patients showed adequate hormonal response to hyperkalemia. This finding is compatible with that reported by Weidmann et al. (14), indicating that high aldosterone secretion plays an important role in maintaining K^+ homeostasis.

Three patients in our study had hyperglycemia while receiving intravenous hyperalimentation and one had hyperglycemia due to uncontrolled diabetes. Hyperglycemia causes a cellular shift from ${K^+}_I$ to ${K^+}_O$, as reported by Seldon and Tarail (15) and Brown (16). Elevated ECF osmolality is also known to lead to K^+ loss from cells.

Conclusions

Hyperkalemia ($K^+ > 5.5$ mEq/L) is a relatively common finding in the adult hospitalized population, as a result of a variety of conditions, such as end-stage renal disease, iatrogenic factors, hyporeninemic hypoaldosteronism, and acute renal failure. Elderly patients—because of their increased incidence of concomitant diseases—have a greater predisposition to hyperkalemia. End-stage renal disease was the most frequent finding in those 60 years or less (68.7%). Iatrogenic causes of hyperkalemia ranked high (43.6%) in the older population. The use of K^+ supplementation and K^+-sparing diuretics in the presence of moderate renal failure were the most frequent iatrogenic causes of hyperkalemia in the elderly. The use of these supplements in the presence of renal impairment is not advisable.

The use of nonsteroidal antiinflammatory agents, angiotensin-converting enzyme inhibitors, and drugs that suppress the renin-aldosterone response should be followed by serial electrolyte determination.

The syndrome of hyporeninemic hypoaldosteronism is observed more commonly in the elderly diabetic patient with moderate renal insufficiency. Most patients with end-stage renal disease showed adequate hormonal response to hyperkalemia. Hyperalimentation may give rise to hyperkalemia; hence, these patients also require close monitoring of their serum K^+.

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Anxiety and the Cardiovascular System

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The manifestations of anxiety often lead individuals to seek medical attention for symptomatic relief, or to be referred for psychiatric care because the signs and symptoms of anxiety complicate the treatment of other conditions. The goal of this paper is to review the features of anxiety and place them in the context of their relationship to the cardiovascular system.

Definition and Prevalence of the Problem

Anxiety may be defined as the subjective experience of dread and foreboding that occurs in association with a variety of autonomic signs and symptoms (1). It differs from fear in that fear is the subjective experience of dread and autonomic arousal that occurs in the presence of a threatening external event (2). Fear would be the expected response to being chased by a bear in a forest, whereas anxiety would be the experience of an individual who perceives the same dread and autonomic arousal during an uneventful trip to the supermarket.

The presence of anxiety does not always signify a pathologic state; anxiety can be a normal and adaptive response to stress that facilitates coping (3). Anxiety is judged to be pathologic when it becomes autonomous (when it appears to have a life of its own), when its intensity is so severe that physicians feel compelled to relieve it, when it persists, and when normal function is impaired by ineffective coping mechanisms (as in avoidance behavior) (3).

Anxiety can be categorized as being acute (a state disturbance) or chronic (a trait disturbance) or by onset in the presence of specific stimuli, as in a phobia (2). Moreover, anxiety may be the sole manifestation of a problem, or it may be symptomatic of a psychiatric (e.g. panic disorder) or a medical (e.g. hyperthyroidism) illness.

The physical signs and symptoms of anxiety (Table 1) are varied. However, most fall within the domain of the cardiovascular system and are a consequence of arousal of the autonomic nervous system.

The range of these symptoms and the fact that they may herald severe medical illness makes it easy to understand why so many individuals seek medical attention when they become anxious. Anxiety disorders have been reported in 5%–14% of general medical outpatients and 5%–20% of medical inpatients (4). Just as important is the fact that anxiety or psychiatric disorders are common initial symptoms of medical illnesses (3, 5–7).

Psychiatric Disorders and Cardiac Symptoms

Physicians have realized for many years that patients often attribute symptoms to their hearts in the absence of significant or identifiable cardiac pathology. Unfortunately, failure to recognize an individual's psychopathology may result in inappropriate hospitalizations or repeated diagnostic testing that is unnecessary, costly, and potentially harmful.

Several psychiatric conditions commonly lead patients to seek medical attention for somatic complaints. These include hypochondriasis, somatization disorders, anxiety disorders, and depression. Each of these disorders is common in patients who complain of chest pain in the absence of significant coronary artery disease. It has been reported that 10%–14% of patients who come to a cardiologist's office have anxiety-derived complaints (3). The physician who recognizes that psychiatric disorders (including anxiety disorders, affective disorders, so-

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matoform disorders, factitious disorders, and complex partial seizures) may be manifested initially by cardiovascular symptoms will be better able to prescribe specific treatment for his or her patient. Each of these psychiatric disorders is reviewed below.

Anxiety Disorders

According to the *Diagnostic and Statistical Manual, Third Edition Revised* (DSM IIIR) of the American Psychiatric Association (8), anxiety disorders are characterized by symptoms of anxiety or avoidance behavior, or both. Disorders that comprise this group include panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without a history of panic disorder, social phobia, simple phobia, obsessive compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and anxiety disorder not otherwised specified.

Anxiety is the predominant symptom in panic disorder and generalized anxiety disorder, whereas avoidance behavior predominates when agoraphobia and phobias occur. In phobic disorders, anxiety increases when the afflicted individual confronts the feared object or situation, whereas in obsessive compulsive disorder it increases when the individual attempts to resist giving in to the obsession or compulsion.

Through the years physicians have used various labels for patients with cardiovascular symptoms in the absence of known cardiovascular disease. These labels have included soldier's heart, DaCosta's syndrome, neurocirculatory asthenia, neurasthenia, and irritable heart (5, 9); physicians have also called these patients "cardiac cripples." Although many of these labels have generated a certain amount of enthusiasm because of their intriguing connotations, the terms have done little to establish the pathophysiology of the problem or specify a more appropriate line of treatment. More recently, a substantial number of patients who manifest cardiovascular symptoms in the absence of cardiac disease have been shown to meet criteria for panic disorder. Fortunately, advances in psychopharmacologic (10, 11) and behavioral techniques (12) have made panic disorder a readily treatable entity.

Panic Disorder without Agoraphobia. The hallmark of this syndrome is the presence of recurrent panic attacks, that is, discrete episodes of intense fear or discomfort in addition to at least four other characteristic symptoms (Table 2). The diagnosis is made only when an organic etiology has not been found to initiate and maintain the disorder. Typically, panic attacks last for several minutes; rarely they may continue for several hours. Early in the course of the disorder, the attacks are unexpected; later, however, symptoms arise in certain characteristic situations (for example, driving over bridges). Not uncommonly, people with panic disorder begin to fear having another panic attack in those situations associated with prior episodes. Between attacks, individuals are often apprehensive and focus on the fear of having another attack.

The disorder commonly begins during the third decade with panic attacks that occur several times a week or even a day; the disorder may last for several years with varying periods of partial or full remission. During these phases, limited-symptom attacks, which induce fewer than four symptoms, may occur. Because of the severity of the symptoms, many individuals have been known to self-medicate themselves with alcohol or anxiolytic agents.

Panic disorder without agoraphobia is thought to be equally common among men and women and occurs less frequently than does panic disorder with agoraphobia. Predisposing factors have been considered to include separation anxiety disorder of childhood, a sudden loss of social supports, or interruption of current interpersonal relationships (8).

Panic Disorder with Agoraphobia. In addition to the criteria for panic disorder as described in Table 2, those patients who have panic disorder with agoraphobia also have a fear of being in places or situations from which escape might be difficult (or embarrassing), or in which help might not be available in the event of a panic at-

TABLE 1
Physical Signs and Symptoms of Anxiety

Anorexia
Butterflies in stomach
Chest pain or tightness
Diaphoresis
Diarrhea
Dizziness
Dyspnea
Dry mouth
Faintness
Flushing
Headache
Hyperventilation
Lightheadedness
Muscle tension
Nausea
Pallor
Palpitations
Paresthesias
Sexual dysfunction
Stomach pain
Tachycardia
Tremulousness
Urinary frequency
Vomiting

Adapted from Rosenbaum JF, Pollack MH. Anxiety. In: Hackett TP, Cassem NH, eds. The Massachusetts General Hospital Handbook of general hospital psychiatry. Littleton MA: PSG Publishing, 1987:154–183.

tack. Patients with this syndrome are often unable to leave the safety of their home environment and therefore delay or avoid attention to their medical needs.

Many patients who have panic attacks have symptoms that mimic the manifestations of physical disorders. Afflicted individuals typically come for evaluation to an emergency room or outpatient medical setting and seek the attention of a general practitioner, cardiologist, or neurologist. Illnesses and/or syndromes having anxiety-like symptoms can be categorized by the organ system primarily involved (Table 3).

Although the pathophysiology of panic attacks is still not entirely clear, it is thought to result from abnormal central nervous system noradrenergic function, that is, an altered sensitivity of noradrenergic receptors in the locus ceruleus (13, 14). The locus ceruleus is a midbrain nucleus that contains 60%–70% of the brain's noradrenergic neuron cell bodies and sends axons to limbic areas responsible for the experience of anxiety.

Treatment of Panic Disorder. Several different treatment modalities, used separately and together, have been effective in the treatment of panic disorder. These modalities include psychotherapy, which is intended to uncover and correct emotional responses to psychologic loss and to restore confidence. Behavioral therapy, including the technique of desensitization, progressively increases one's exposure to a given anxiety-provoking situation or stimulus so that mastery may be achieved and anxiety minimized (12).

A variety of antidepressant medications have also been employed, usually at "full therapeutic" doses (10). These agents include the commonly prescribed tricyclic antidepressant agents (for example imipramine, usually at doses greater than or equal to 150 mg/d). Monoamine oxidase (MAO) inhibitors, such as phenelzine (typically at doses approaching 15 mg/kg per day), are often used to treat both depressive symptomatology and panic-related symptoms (11). More recently, the high-potency benzodiazepines, such as alprazolam (typically used in doses of between 2 and 8 mg/d) and clonazepam (typically used at doses of 2–4 mg/d), have been effective in relieving the acute symptoms of panic attacks (11, 15). In addition, beta-blocking agents, for example propranolol, have also been used to block the peripheral manifestations of anxiety. This effect may result in a sense of comfort and confidence in the patient that further minimizes the prevalence of panic attacks.

TABLE 2

Diagnostic Criteria for Panic Disorder

A. At some time during the disturbance, one or more panic attacks (discrete periods of intense fear or discomfort) have occurred that were (1) unexpected, i.e. did not occur immediately before or on exposure to a situation that almost always caused anxiety, and (2) not triggered by situations in which the person was the focus of others' attention.

B. Either four attacks, as defined in criterion A, have occurred within a four-week period, or one or more attacks have been followed by a period of at least a month of persistent fear of having another attack.

C. At least four of the following symptoms develop during at least one of the attacks:

1. Shortness of breath (dyspnea) or smothering sensations
2. Dizziness, unsteady feelings, or faintness
3. Palpitation or accelerated heart rate (tachycardia)
4. Trembling or shaking
5. Sweating
6. Choking
7. Nausea or abdominal distress
8. Depersonalization or derealization
9. Numbness or tingling sensations (paresthesias)
10. Flushes (hot flashes) or chills
11. Chest pain or discomfort
12. Fear of dying
13. Fear of going crazy or of doing something uncontrolled

Note: Attacks involving four or more symptoms are panic attacks; attacks involving fewer than four symptoms are limited-symptom attacks.

D. During at least some of the attacks, at least four of the C symptoms developed suddenly and increased in intensity within ten minutes of the beginning of the first C symptom noticed in the attack.

E. It cannot be established that an organic factor initiated and maintained the disturbance, e.g. amphetamine or caffeine intoxication, hyperthyroidism.

Note: Mitral valve prolapse may be an associated condition, but does not preclude a diagnosis of panic disorder.

Reprinted from American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders. Third Edition, Revised. Washington, D.C.: American Psychiatric Association, 1987.

Finally, in the small subset of patients whose panic attacks are secondary to complex partial seizures, antiseizure medications such as carbamazepine may be efficacious.

Generalized Anxiety Disorder. Another of the conditions signalled by anxiety and somatic manifestations is generalized anxiety disorder. In this disorder, excessive anxiety and worry about two or more life circumstances occurs in the presence of, or associated with, the signs and symptoms of motor tension, autonomic hyperactivity (sweating, tachycardia, hyperventilation, tremulousness, dizziness), and heightened vigilance (irritability, exaggerated startle response, feeling on edge). It is distinguished from panic disorder by chronic and persistent rather than episodic symptoms. The treatment of generalized anxiety focuses on the judicious use of anxiolytic medications and behavioral or psychotherapeutic techniques that promote relaxation and reduce anxiety.

Affective Disorders

This diagnostic category includes bipolar (manic-depressive) illness as well as a variety of conditions with depressive symptomatology (including major affective disorder, depressed type). Patients with these disorders commonly have physical complaints; moreover, depressive illness may coexist with panic attacks.

Somatoform Disorders

Patients having somatoform disorders also seek medical attention because of physical complaints and anxietylike symptoms. The essential features of this group of disorders are physical symptoms that suggest a physical disorder in the absence of demonstrable organic findings or known physiologic mechanisms, and for which there is evidence or presumption of an underlying psychologic conflict. Within this diagnostic grouping, patients with hypochondriasis plague physicians most severely.

Hypochondriasis. The features of hypochondriasis include an unrealistic interpretation of physical signs and symptoms as being abnormal, a fear of disease and a conviction that one is sick, a preoccupation with one's body, and a persistent and unsatisfactory pursuit of medical care despite medical diagnostic testing and reassurance. Patients with hypochondriasis in the presence of cardiac complaints have been considered to have a cardiac neurosis.

Somatization Disorder. Less commonly, patients with a somatization disorder—a diagnosis that depends on the presence of multiple symptoms (more than twelve in men and fourteen in women)—whose complaints are chronic, dramatic, and may vary have been known to seek cardiologic care.

Somatoform Pain Disorder. Patients having a somatoform pain disorder may also have cardiac complaints. The diagnosis entails a singular complaint of pain, in the absence of adequate physical findings, and a suspicion that there is psychologic etiology.

Factitious Disorders

Factitious disorders have been thought by many to be uncommon. However, patients with factitious illness often present diagnostic dilemmas for clinicians. This group of disorders has also been known as Münchausen's syndrome, or cardiopathica fantastica when cardiac symptoms (chest pain, rhythm disturbances) prevail. These patients often present with detailed and grandiose stories, a lack of social supports, extensive travel and have personality disorders typically manifested by hostility, masochism, and poor impulse control (16).

Complex Partial Seizures

A neuropsychiatric diagnosis, complex partial seizures, accounts for a minority of patients with anxietylike symptoms who seek medical and cardiac attention. Patients with this disorder may have chest pain, tachyarrhythmias, and syncope due to bradycardia or sinus arrest. The diagnosis is a clinical one that can be facilitated by electroencephalographic findings and a therapeutic response to anticonvulsants (but not to antianginal medications).

Psychiatric Risk Factors for Cardiac Disease

Practitioners of internal medicine and psychiatry have long recognized that cardiac patients exhibit certain characteristic emotions and patterns of coping, for example worry (17), joyless striving (18), suppression of anger (19). In addition, both acute and chronic psychologic distress have often been noted to precede myocardial infarction (MI) (20), cardiac arrhythmias (21, 22), and sudden cardiac death (23, 24). As a result of these observations, researchers have sought to delineate specific risk factors for cardiac symptomatology and cardiac disease. A lack of social support (25, 26), bereavement (27, 28), and an accumulation of stressful life events (29) have all been identified as risk factors for cardiac events.

The physiologic changes associated with stressful events or circumstances involve an acute flight-or-fight reaction that leads to arousal or activation of the sympathetic nervous system. Elevations in catecholamines, epinephrine and norepinephrine, will lead to increases in heart rate, cardiac contractility, and cardiac output, as well as peripheral resistance. In addition, both

TABLE 3

Physical Causes of Anxietylike Symptoms

Type or Cause	Specific Cause
1. **Cardiovascular**	angina pectoris, arrhythmia, congestive heart failure, hypertension, hypovolemia, myocardial infarction, syncope, valvular disease, vascular collapse
2. **Dietary**	caffeinism, monosodium glutamate, vitamin deficiency diseases
3. **Drug related**	akathesia, anticholinergic toxicity, digitalis toxicity, hallucinogens, hypotensive agents, stimulants, withdrawal syndromes
4. **Hematologic**	anemias
5. **Immunologic**	anaphylaxis, systemic lupus erythematosis
6. **Metabolic**	hyperadrenalism, hyperkalemia, hyperthermia, hyperthyroidism, hypocalcemia, hypoglycemia, hyponatremia, hypothyroidism, menopause, porphyria
7. **Neurologic**	encephalopathies, essential tremor, intracranial mass lesions, postconcussion syndrome, seizure disorders, vertigo
8. **Respiratory**	asthma, chronic obstructive pulmonary disease, pneumonia, pneumothorax, pulmonary edema, pulmonary embolism
9. **Secreting Tumors**	carcinoid, insulinoma, pheochromocytoma

Reprinted from Rosenbaum JF. The drug treatment of anxiety. N Engl J Med 1982; 306:401–404.

systolic and diastolic blood pressures will increase and the threshold for ventricular fibrillation will decrease.

When stress on the individual is chronic, a chronic state of vigilance will occur. In this situation there will be activation of the pituitary-adrenal cortical system leading to elevations in corticosterone, platelet mass, the potential for cardiovascular disease, blood pressure, potassium excretion, cholesterol, and a sensitivity to catecholamines (29).

Type A Behavior Pattern. The Type A, or coronary-prone, behavior pattern has been thought to be a risk factor for coronary artery disease ever since it was first described in 1959 by Friedman and Rosenman (30). This behavior pattern is manifest by a sense of competitiveness, excessive drive, an enhanced sense of time urgency, and unexpressed hostility. More recent research has suggested that it is not the Type A behavior pattern itself, but the unexpressed hostility, that may be most relevant to increased risk of cardiovascular disease (31–33). Although few physicians would dispute the existence of a Type A behavior pattern, some controversy continues as to its relative contribution to risks for coronary artery disease (34). The pattern can be modified with individual and group therapies (35–37). Several studies have detected a decrease in the prevalence of recurrent nonfatal myocardial infarction after effective use of these techniques (35–37).

In general, Type A people exhibit more vigorous cardiovascular and neuroendocrine responses to stress (38–40) (mental work), possibly leading to increases in epinephrine, norepinephrine, cholesterol, heart rate, and blood pressure. They may also have a tendency toward a lower threshold for ventricular fibrillation (41).

Psychiatric Symptomatology and Cardiac Disorders

Several discrete cardiac conditions and disorders have been associated with a wide variety of psychiatric symptomatology. Although most cardiac patients ultimately adjust well to their illness, in the acute phase a significant proportion develop anxiety, depression, behavioral abnormalities, agitation, or delirium. Among these conditions, myocardial infarction, ventricular tachyarrhythmias, cardiac surgery, mitral valve prolapse, and silent ischemia have received the greatest deal of attention in recent years.

Myocardial Infarction

Preadmission Phase. Each year in this country alone several hundred thousand individuals suffer from myocardial infarction (MI) (42). Unfortunately, most deaths secondary to acute attacks occur during the first four hours after infarction as a result of arrhythmias or pump failure, or both (43). The time between the onset of chest pain and arrival at the hospital is often prolonged, secondary to a state of psychologic denial (44). A study at the Massachusetts General Hospital by Hackett and Cassem (44) found that the mean time between onset of chest pain and arrival at the hospital was 3.9 h. Authors Hackett and Cassem (44) consider that in many subjects a delay in seeking medical attention was a result of denial—"the conscious or unconscious repudiation of all or part of the total available meaning of an event to allay fear, anxiety, or other unpleasant affects" (45). Since this delay in receiving appropriate medical attention frequently leads to increased morbidity and mortality, physicians' actions that minimize this denial in the preadmission phase are reasonable. Education of patients and their relatives about the nature and timing of cardiac symptoms should help to decrease untoward outcomes.

Emergency Room Phase. Once the patient has overcome his or her denial and arrives at the Emergency Room (ER) for medical attention, the most common emotions include anxiety and fear. Anxiety arises because of the fear of death, and may be exacerbated by the presence of ongoing chest pain and shortness of breath and the recollection of previous cardiac admissions.

Anxiety may be heightened when an individual is subject to an array of high-technology procedures. Patients in the ER have intravenous lines placed, undergo cardiac monitoring, and are often prepared for emergency or semiemergency trips to the cardiac catheterization laboratory so that thrombolytic techniques (streptokinase, tissue plasminogen activator) or percutaneous angioplasty can be performed. When patients are not being bombarded by high technology and invasive cardiac maneuvers, their imaginations often run rampant, increasing their fears.

Anyone directly or even indirectly associated with the care of the MI patient should maintain a sense of calm that can be transmitted to the patient. The administration of the sacraments to the sick has been shown to increase anxiety in some patients (46). If family members of the patient are uninformed, they are at risk for transmitting their apprehension to the patient. As a result, even brief, limited explanations will serve to decrease the tension surrounding the patient's admission for acute MI.

Coronary Care Unit Stay. During an individual's coronary care unit (CCU) stay for the treatment of MI, several psychiatric states and conditions tend to prevail, including anxiety, depression, delirium, and the manifestations of premorbid characterologic states (47). Typically, each of these conditions will manifest itself in certain characteristic time frames (47).

According to Cassem and Hackett (47), psychiatric consultations for problems related to anxiety in the CCU occurred most often on the first two days of a patient's admission. Patients' signs and symptoms of anxiety while in the CCU are similar to or even identical with those suffered by patients having chest pains secondary to MI, congestive heart failure, or cardiogenic shock; the nature of such symptoms (Table 1) must be taken in the context of the clinical situation.

Depression is a common complication of MI (47). In Cassem and Hackett's study, depressive symptomatology leading to psychiatric consultation was most often manifest on the third and fourth days of a patient's stay in the CCU (47). Although many individuals will have some features of depression, a diagnosis of major affective disorder, depressed type, is probably uncommon in the acute phases of MI. A diagnosis of major depression requires that several diagnostic criteria be fulfilled (8). Among these are a sleep disturbance (usually decreased sleep with early morning awakening), a decrease in interests, a sense of guilt or a preoccupation of thought (usually a preoccupation with bodily concerns), a decrease in energy, a decrease in ability to concentrate, a disturbance of appetite (usually decreased, in association with weight loss), the presence of psychomotor agitation or retardation, and suicidal thoughts or thoughts of death. The presence of four or more of these eight symptoms in association with depressed mood for a duration of two weeks or greater are the criteria for major affective disorder, depressed type.

Delirium is manifested by clouded consciousness, disorientation, memory disturbance, perceptual disturbances (illusions, hallucinations), rapid or incoherent speech, a state of agitation, and a disturbance of the sleep-wake cycle (8). Frequently these features fluctuate over the course of hours. Although delirium may develop at any point during the course of a seriously ill patient's stay in the CCU, at the Massachusetts General Hospital it tends to occur in a bimodal distribution. One subset of patients tends to become delirious on arrival in the CCU in the setting of cardiogenic shock and high-dose antiarrhythmic therapy. It is not uncommon for clinicians to misdiagnose this syndrome, diagnosing anxiety instead of delirium (48). Symptoms of delirium are rarely due to the patient's unfamiliarity with the hospital environment; accurate diagnosis is essential so that specific etiologies can be specifically treated (48).

Inappropriate or disruptive behavior generally surfaces after several days in the CCU (47).

Most of these can be understood in the context of the patient's personality and typical response to stressful circumstances (49). Seven distinct personality styles (paranoid, schizoid, oral-dependent, hysterical, narcissistic, obsessive, and masochistic) have been identified, each having a characteristic reaction to illness (50). Moreover, management strategies have been devised to help caregivers address the specific needs of each personality type (51). Failure to address these issues will lead to heightened anxiety among patients with MI.

Ventricular Tachyarrhythmias

Individuals who are subject to recurrent symptomatic ventricular ectopic activity (VEA) often have acute and chronic anxiety that can lead to extreme apprehension, resistance to sedation, and a fear of sleep. The arrhythmias experienced by some of these patients are precipitated by sudden emotional stress (52, 53). Many of these patients try to minimize uncertainty and learn relaxation techniques that will at least theoretically raise their threshold to ventricular fibrillation. VEA may also herald cardiac arrest. This state may result in subtle or profound neurologic deficits that are associated with psychiatric symptomatology, including organic brain syndromes, nightmares, personality disturbances, and poor social functioning (54).

In the hospital setting, many patients who have had out of hospital cardiac arrest, or malignant VEA undergo electrophysiologic studies in the catheterization suite. In patients, these intense, physically taxing, repetitious evaluations are often associated with impatience, irritability, behavioral regression, and physical deconditioning. Much of the anticipatory anxiety experienced by these patients is associated with a pass-fail mentality. In our experience, treatment with any of a number of anxiolytics and supportive psychotherapy has been useful.

Cardiac Surgery

Psychiatric manifestations related to cardiac surgery occur in the preoperative, immediate postoperative, and long-term recovery phases. In the preoperative phase, anxiety is prominent. It can be minimized by preoperative instructions and motivation of the patient and by providing family and social support (55, 56).

In the immediate postoperative phase, delirium is the most important psychiatric complication. It is also more common than anxiety or depressive reactions. Delirium in this time frame has been noted to occur in 11%–28% of patients undergoing coronary artery bypass grafting (57, 58) and 18%–24% of patients undergoing cardiac transplantation (59–61).

After successfully undergoing cardiac surgery, a majority of individuals are able to resume normal psychologic, social, and economic functioning; only 5% show continuing substantial performance decline six months following surgery (62).

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is a condition of invagination or herniation of the valve leaflets backward into the left atrium during left ventricular systole (63). MVP commonly occurs among patients with anxiety syndromes, often characterized by hyperdynamic beta adrenergic secretion. Since the symptoms that occur in patients with MVP (palpitations, tachycardia, chest pain) are often the same as the symptoms of panic disorder, MVP has been thought to coexist with panic disorder (64). However, treatment of the symptoms associated with MVP will in general not prevent panic attacks. This leads some investigators to believe that panic disorder and MVP are different manifestations of an autonomic dysfunction that is common to both syndromes (65). Frequently, reassurance that is given to patients who have MVP is sufficient to minimize their apprehension and need for subsequent visits for fears associated with cardiac symptomatology. If MVP and panic attacks coexist, treatment should be directed at the prevention of arrhythmias, infectious complications, and panic. Several effective antipanic medications—high-potency benzodiazepines (alprazolam and clonazepam), tricyclic antidepressants, or MAO inhibitors—are available.

Silent Ischemia

Over the last several years investigators have demonstrated that a substantial number of patients with coronary artery disease (CAD) manifest silent myocardial ischemia (66). The use of Holter monitoring of ST segments in patients with known, symptomatic CAD indicates that many episodes of ischemia occur during everyday life. Commonly, nonpainful ischemia occurs in the absence of clearcut precipitants. Investigators using noninvasive positron-emission tomography with rubidium 82 to assess myocardial perfusion in angina patients have delineated that simple mental stress is capable of causing silent disturbances of regional myocardial perfusion (66). Since many of these ischemic episodes occurred at substantially lower heart rates than those occurring during physical exercise, the underlying mechanism of ischemia requires further study. Although the clinical implications of silent ischemia have not been well elucidated, there is reason to believe that treatment with anxiolytic medications of even nonsymptomatic CAD patients might lead to a reduced incidence of silent ischemic episodes, catastrophic arrhythmias, and infarctions (66).

Psychotropic Agents in Patients with Cardiac Disorders

Psychotropic agents and electroconvulsant therapy (67) exert important effects on the cardiovascular system. Consequently, many physicians are reluctant to prescribe these treatments for the elderly or for those at risk for or already manifesting cardiovascular disease. Although a complete review of this subject is beyond the scope of this paper, several classes of medications commonly used to treat anxiety, and depressive syndromes associated with anxiety, are discussed.

Minor Tranquilizers. Benzodiazepines have replaced the barbiturates as the drugs of choice for the treatment of anxiety syndromes (68, 69). These agents may be distinguished from one another by virtue of their side-effect profile (49). They differ in onset and duration of action, degree of sedation they cause, potency, and method of metabolism and excretion.

These agents are safe and have beneficial effects on cardiovascular function. Intravenously administered diazepam has been shown to have a nitroglycerin-like action on the coronary and systemic circulation, resulting in decreased myocardial oxygen consumption (MVO_2) without modification of either coronary blood flow or coronary vascular resistance (70); midazolam produces even greater reduction in MVO_2 (71). Intravenous midazolam and diazepam (72) and oral alprazolam (73) decrease sympathetic tone. This may be helpful in the care of patients with elevated circulating levels of catecholamines (acute MI or congestive heart failure), or in patients with coronary artery spasm whose coronaries contain excessive stores of catecholamines (74).

Antidepressants. Antidepressants, classes of drugs that include the traditional tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, psychostimulants, and lithium carbonate, are the drugs of choice for the treatment of depressive syndromes. Other indications include headache, chronic pain, and panic disorder with or without avoidance behavior.

The side-effect profile is important in patients with cardiovascular disorders (75–78). The tricyclic antidepressants have the ability to cause hypotension, to increase heart rate by virtue of their anticholinergic effects, to affect the cardiac conduction system (like the Type 1 antiarrhythmic drugs such as quinidine), and to cause varying degrees of sedation. Safe prescription of these agents is possible if their cardiovascular effects are understood and monitored appropriately. In general, the tertiary amines (amitriptyline, doxepin, imipramine) more commonly cause orthostatic hypotension and a greater degree of tachycardia. Their active metabolites, the secondary amines (nortriptyline, desipramine, protriptyline), minimize these side effects.

The MAO inhibitors, generally a second-line treatment for depression and panic attacks, commonly cause orthostatic hypotension. This makes their use problematic for patients with ischemic heart disease.

Other psychotropic agents, including carbamazepine, lithium carbonate, and the psychostimulants, each have their place in the treatment of affective states in cardiac patients. However, these agents are not typically used for the treatment of anxiety.

Conclusion

An awareness of the spectrum of symptoms associated with anxiety syndromes will lead to more effective treatment of the anxious patient. Knowledge that a host of psychiatric disorders and conditions may initially entail cardiac symptomatology will help physicians avoid nonessential invasive workups and apply appropriate pharmacologic and nonpharmacologic interventions in their stead. Determination of the presence or absence of psychologic risk factors for the development of cardiac disease will also enable patients and physicians to minimize those risk factors. The detection of psychiatric symptomatology among patients with cardiac disorders will lead physicians to refer their patients for psychiatric consultation and to institute timely interventions. Finally, the appropriate use of psychotropic agents in patients with cardiac disorders will contribute to a decrease in patient morbidity and mortality.

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Special Rheumatologic Problems of Older People

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Although it is true that there is an age predilection for various rheumatic diseases, almost any one of those disorders can occur in older people (defined as over age 60). Even Still's disease, or juvenile rheumatoid arthritis, exists in an adult form (1). On the other hand, such rheumatic conditions as polymyalgia rheumatica occur almost exclusively in the older population. We must therefore consider the special problems in senior citizens of virtually the whole gamut of rheumatologic disorders.

Because that task is clearly impossible in this relatively brief communication, I deal here with certain specific problems which impact on the aged. These include the special diseases of the elderly; the peculiar age-specific aspects of more common forms of arthritis; the precautions and caveats necessary in applying various therapeutic modalities; and the social impact of arthritis on the aged person.

Special Rheumatologic Diseases of Older Persons

Calkins in 1982 (2) published an excellent review of three rheumatic diseases that are virtually unique to the elderly population: pseudogout, polymyalgia rheumatica, and giant-cell arteritis (the latter two being perhaps related).

Pseudogout. Pseudogout, or chondrocalcinosis, is a subset of osteoarthritis associated with the radiologically visible deposition of calcium (in various combinations) in the articular cartilage. The course of this disorder often includes synovial flareups that somewhat resemble acute gout, but in pseudogout the examination of synovial fluid fails to reveal urate crystals and the response to colchicine is equivocal at best.

The differential diagnosis between gout and pseudogout must be made, since the treatment of the two is quite divergent, but differentiation is sometimes difficult because many elderly persons take thiazide diuretics, which elevate serum uric acid levels. One must constantly be on guard against making a presumptive diagnosis of classical gout in any patient with synovitis and high serum uric acid. Examination of joint fluid for crystals is the easiest and most reliable way to be sure.

Polymyalgia Rheumatica and Giant-Cell Arteritis. Polymyalgia rheumatica (PMR) and giant-cell arteritis (GCA) have probably always been with us, but their existence in the United States was called to our attention by the first published cases in this country by Calabro (3) in 1962 and by Davison, Spiera, and Plotz (4) in 1966. These possibly related conditions occur almost exclusively in the elderly, often have dramatic initial symptoms, and can be treated effectively, often with a dramatic response.

PMR usually has an acute specific onset, unlike the vague creakiness of old age. The predominant symptom is pain, especially in the musculature about the pectoral and pelvic girdles. There is no true limitation of motion, and various tests of muscle involvement are unrevealing. The question of whether or not there is in PMR an underlying nonspecific synovitis, particularly of the shoulders, is unresolved; some claim that joint scintigraphy and other techniques demonstrate synovitis, and others deny its presence.

The cardinal laboratory test is the sedimentation rate, which is usually markedly elevated,

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sometimes to a level of 100 mm/h or greater (Westergren method).

PMR is one of the rare benign diseases in which the use of corticosteroids is clearly indicated. Relatively small doses of prednisone—at levels of 10 mg/d or less—produce dramatic relief of symptoms, fall in sedimentation rate, and protection against the ocular component of GCA.

GCA is present in perhaps 30% of patients with PMR, as demonstrated by temporal-artery biopsy, but—fortunately—ocular symptoms occur with far less frequency. In the event that they do occur, the dose of prednisone must be increased immediately to 40–60 mg daily, and ophthalmologic consultation should be sought.

A rare form of arthritis called Jaccoud's arthritis may occur in elderly people. This is a noninflammatory development of ulnar drift of the fingers and hands often associated with adult rheumatic fever and systemic lupus. Excellent reviews of the subject by Villaiumey (5) and by Bywaters (6) have recently been published.

Age-Specific Aspects of Arthritis

Turning to more common forms of arthritis which have special facets in elderly persons, we must consider rheumatoid arthritis (RA), osteoarthritis (OA), and gout.

Rheumatoid Arthritis. RA is often thought to be primarily a disease of young or young-middle life. Although the prevalence of RA may be greater in younger people (there are more of them), the incidence of this condition is probably pretty much the same throughout adult life. Healey (7) has reviewed this problem and has divided rheumatoid arthritis in the elderly into various subsets, including classic seropositive RA, "seronegative benign synovitis" (he includes PMR in this group), and Sjogren's syndrome with arthritis.

Deal et al. (8) compared 78 elderly-onset RA patients with 134 younger-onset patients, and noted various differences. The older group more often appeared initially to resemble PMR patients, were less likely to have subcutaneous nodules, and generally had a more benign course with significantly better prognosis. On the other hand, many authors have noted the increased risk of gastrointestinal bleeding and other side effects in older RA patients taking nonsteroidal antiinflammatory drugs or disease-modifying agents.

Osteoarthritis. Osteoarthritis, almost by definition, occurs with aging-related increasing frequency. That this is not a straight-line increase in incidence, however, was demonstrated by Forman et al. (9), who studied osteoarthritis of the knee in 682 elderly people. They showed that the severity and frequency of symptoms and signs was reasonably constant in the seventh, eighth, and ninth decades, indicating that the condition was not inevitably progressive. They showed also that the incidence was higher in women than in men, and in blacks than in whites, although these findings may have been related to the risk population in the study and the self-selection process of the patients studied.

In any event, many studies have suggested that osteoarthritis (OA) is multifactorial and not simply the inevitable consequence of wear and tear over time. Wilkins et al. (10) have shown that about a third of the patients in a geriatric unit had radiologic evidence of articular chondrocalcinosis (pseudogout) and that the development of chondrocalcinosis was age related. About three quarters of the patients with chondrocalcinosis also had OA in the affected joint, and the combination of OA and chondrocalcinosis was more frequently associated with local inflammation than was OA alone.

Gout. Gout developing after age 60 is being seen with far more frequency than twenty years ago, most likely because of the increased use of thiazides. Ter-Borg and Rasker (11) analyzed 40 patients older than 60 years of age who had gout and found slightly more than half to be women. The disease tended to be polyarticular, although the hallux joint was commonly affected, and, in women, finger involvement was relatively common. About half of the men and virtually all of the women were taking diuretics. This observation has been generally confirmed, and MacFarlane and Dieppe (12) conclude that elderly women are particularly likely to develop diuretic-induced tophaceous gout but seem less likely to develop acute attacks than men. In general, uric acid levels were elevated, more so in women than in men.

It is important, in elderly people with polyarthritis, to consider the possibility of gout and, in women particularly, to be careful to distinguish finger tophi from Heberden's nodes.

Therapy for Older Persons

Therapy for rheumatic disease in the elderly is particularly challenging. Clearly, the result of aging in many people is a diminution in renal and hepatic function, which is bound to affect drug metabolism. In addition, we are dealing with people who have had many years of insults to the gastrointestinal tract, and this too affects drug tolerance.

Nonsteroid Antiinflammatory Drugs and GI Bleeding. Perhaps the most comprehensive study of acute gastrointestinal bleeding in the elderly was conducted by Alexander et al. (13), who analyzed the records of 1,878 hospitalized patients to find those older than age 75 who had acute hematemesis. There were 93 such patients, and one-third of them had been taking nonsteroidal antiinflammatory drugs (NSAIDs), specifically ibuprofen, indomethacin, or aspirin. This incidence was far higher than in the nonbleeders and demonstrates the need for protection of the gastric mucosa in elderly persons who are taking NSAIDs. Fortunately, there are now available many modalities for such protection, ranging from simple antacids to cytoprotection, and it seems likely that their increased use will lead to a decline in acute gastrointestinal bleeding emergencies.

Renal Effects. A certain amount of controversy has centered on the renal effects of various NSAIDs but there seems to be general agreement that those effects may be dose related. Piroxicam in particular should be given with caution to the elderly, and naproxen, as demonstrated by McVerry et al. (14), should also be given at the lower end of the dosage range. Even salicylates have increased toxicity in the elderly, as shown by Grigor et al. (15).

Toxicity of Remittive Drugs. As far as remittive agents are concerned, Kean et al. (16) have shown that people older than 60 years respond to gold as well as younger people do, and toxicity in general occurred with equal frequency. However, they found that serious hematologic toxicity was relatively less frequent under age 47, and nephrotic syndrome did not occur under age 52. In another study, Kean et al. (17) studied the efficacy and toxicity of D-penicillamine for rheumatoid disease in the elderly. They found equal efficacy in older and younger groups but more skin rash and problems with taste in the elderly. Prior treatment with gold did not seem to affect the result.

Treatment with the anticancer agents azathioprine, cyclophosphamide, and methotrexate must be cautious in the elderly, particularly if the physician has any suspicion of renal or hepatic impairment.

Social Impact of Arthritic Diseases

Finally, one must consider the social impact of arthritic diseases in the aged. Chronic pain and impairment of function can be devastating at any age but raise the ugly specter of loss of independence for the elderly person. For this reason aggressive and optimistic management is usually in order for people older than 60 years.

Although corticosteroids are seldom useful in managing rheumatoid arthritis in younger persons, one can relax restrictions somewhat for older people. Small doses of prednisone, under 10 mg daily and given intermittently, can provide a considerable margin of relief and do not pose such a problem of dependency and long-term toxicity. For older persons this treatment may make the difference between a socially useful life and a life of dependency on children or others.

Social Agencies as Treatment Adjuncts. It is wise to become aware of the various social agencies that provide relief for older people. The local chapter of the Arthritis Foundation can provide resources for older patients, and local agencies such as the Visiting Nurse Association may be able to assist with medications and even home physiotherapy. Homemakers and similar forms of asistance are sometimes available through city, county, or state agencies.

In sum, the most important aspect of treating rheumatic disease in the elderly is to treat it—not to look on it as an inevitable and untreatable aspect of the aging process. The attitude of the physician can in itself be therapeutic, because patients will try harder and adhere to a regimen better if they feel that the physician really believes that the program prescribed will be helpful. We do not need to raise false hopes or promise unrealistic results. We simply need to treat our elderly patients positively, optimistically, and cheerfully.

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Avoiding Adverse Drug Reactions in the Elderly

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Adverse drug reactions (ADRs) are responsible for significant morbidity and mortality among the elderly. Even though the elderly comprise 12% of the U.S. population, they consume 25% of all prescription drugs and experience 30% of all ADRs reported to the Federal Drug Administration (1). Early recognition of potential drug–drug and drug–disease interactions is critical if we are to prevent prolongation of hospital stay and also prevent admissions caused by ADRs. This article focuses on the reasons why elderly patients are at higher risk for ADRs: multiple disease states, multiple prescription drugs, and age-related changes in pharmacokinetics and pharmacodynamics.

Definitions

An ADR is defined as any unintended or undesired effect of a drug in a patient (2). This effect, or clinical manifestation, may include abnormal laboratory tests, symptoms, or signs.

Side Effect. According to Seidl and others (3), the most common type of ADR is the side effect, an unintended effect that is not directly related to the drug's primary mechanism of action, is not necessarily dose related, and usually occurs at therapeutic serum concentrations. Examples of this sort of ADR, and of the associated drug or drug class, include

- dry mouth—tricyclic antidepressants
- hypokalemia—diuretics
- gingival hyperplasia—phenytoin

Drug Toxicity. The second most common ADR, drug toxicity, is an undesired effect that is usually directly related to the drug's primary mechanism of action and is dose dependent. Examples include

- excessive daytime sedation—hypnotics
- diarrhea—laxatives
- syncope—antihypertensive agents

Immunologic Reaction. Immunologic reaction is the third most common ADR in the acute-care setting (3). Prior exposure to the drug is usually assumed when hypersensitivity reactions occur but is hard to document. The clinical manifestation (rash, fever, bronchospasm, lymphadenopathy) depends upon the manner in which the host responds immunologically. This ADR is usually unrelated to the known pharmacologic effects of the drug or to its dose. Rechallenge, one of the criteria cited by many as the "acid test" for establishing the presence of an ADR, is usually not recommended in this setting because it could potentially result in anaphylaxis (and possibly death).

Idiosyncratic Reaction. Idiosyncratic reactions are rare, usually unpredictable, ADRs that are unrelated to dose and to the drug's mechanism of action. They are not immunologically mediated. One example:

- agranulocytosis—chloramphenicol

Some reactions that were previously considered to be idiosyncratic are now classified as drug–disease interactions; for example:

- hemolytic crisis—many drugs in patients with G6PD deficiency

Some researchers have postulated that all idiosynchratic reactions are caused by the interac-

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tion of drugs with a single chromosomal abnormality, but most of these reactions are as yet uncharacterized.

Drug–Disease Interaction. Certain drugs are contraindicated in specific disease states because those drugs produce predictable adverse reactions that are not necessarily related to the drug's primary mechanism of action. For example:

- Patients with acute intermittent porphyria can be thrown into crisis by anticonvulsants such as phenobarbital and phenytoin.
- Patients with Alzheimer's-type dementia may develop paradoxical reactions to a variety of psychoactive agents. Benzodiazepines may make these patients more confused and agitated, and drugs with anticholinergic properties (amitriptyline and thiothixene, for example) may exacerbate both the memory and the thought disorder.

Paradoxical drug–disease interactions also include

- quinidine—occasionally exacerbates cardiac arrhythmias

Drug–Drug Interaction. The incidence of drug–drug interactions varies according to the number of drugs used and the care with which ADR etiology is determined. The Boston Collaborative Drug Surveillance Program (2) found that drug–drug interactions were the most common of all ADRs, accounting for 22% of the total identified in a rehabilitation hospital. This number fell to 6.9%, however, when these investigators used the same methods to examine ADRs in an acute hospital setting (4).

Secondary Effect. Some ADRs are secondary to others. For example:

- haloperidol—known to cause drug-induced parkinsonism

This side effect is caused by postsynaptic blockade of striatal dopamine receptors and can be eliminated by either reducing the dose of the drug or by discontinuing it. Haloperidol has recently been reported to increase the risk for radial nerve palsy in nursing home patients. Sloane and McLeod (5) described three elderly women who were demented and confined to chairs most of the day. They tended to lean against arm rests which were at the level of the midhumerus. All three patients developed wrist-drop within a month of starting a regimen of, or being advanced to higher doses of, haloperidol (0.5–2.0 mg/d). All three women improved when the arm rests were padded, the arms were splinted, and the drug was discontinued. Radial nerve compression in these patients was most likely secondary to haloperidol-induced parkinsonism.

Influence of Age on ADRs

Seidl and others (3) showed that 13.6% of patients admitted to an urban American teaching hospital medical service acquired at least one ADR during their hospital stay. The elderly were more vulnerable, the highest ADR rates being found among those in their eighth (18%) and ninth(24%) decades. The average length of stay for patients with ADRs was prolonged (21 days) compared to the average for all patients admitted to acute medical beds (14 days).

Hurwitz (6) studied patients admitted to an acute medical service in Belfast and found that 10% of those given drugs developed ADRs. Just as in Seidl's study, the elderly acquired more ADRs, the highest rates occurring in patients in their eighth (21%) and ninth (19%) decades. The average length of stay for patients experiencing ADRs was longer (21 days) than that for the study population as a whole (15 days). Current pressures toward shorter lengths of hospital stay are forcing us to be even more keenly aware of the need to avoid ADRs.

Williamson and Chopin (7) found that 15.3% of patients admitted to geriatric in-patient services in England, Scotland, or Wales experienced an ADR during their hospital stay. The drugs producing ADRs in this sample reflected the chronic nature of the diseases treated on a geriatric service (antihypertensive, antiparkinsonian, and psychotropic agents). This differed from Seidl's (3) list of drugs most likely to produce ADRs on an acute medical service (antibiotics, cardiovascular agents, sedative-hypnotics, and insulin).

In a careful cross-cultural comparison of acute medical services, Lawson and Jick (8) showed that more American inpatients experienced ADRs (26%) than Scottish in-patients (15%). The authors attributed this to the fact that Americans consumed twice as many drugs as the Scots. This conclusion had further support when it was discovered that there were no cross-cultural differences in the incidence of ADRs with specific drugs (heparin, 14%–15%; furosemide, 12%; digoxin, 11%; ampicillin, 10%–11%).

Drug–Disease Interactions

Diseases of the kidneys and liver can alter the way drugs are cleared from the body. Diseases that affect the way drugs interact with their end-organs are discussed below under the section on pharmacodynamics.

Renal Disease. Although the overall risk of ADRs is not increased by the presence of renal disease (6), such a disorder can be a contributing factor when specific drugs are administered.

- Morphine has an active metabolite that accumulates in patients with renal failure, even though the kinetics of the parent compound remain unchanged (9). These patients may thus develop excessive narcosis with standard therapeutic doses of morphine.
- The excitotoxic metabolite of meperidine (normeperidine) can accumulate with standard doses in patients with renal insufficiency, producing agitation, confusion, tremor, myoclonus, or seizures (10).

Hepatic Disease. Patients with liver disease or heart failure are at higher risk for developing ADRs when they take drugs that depend upon the liver for clearance or metabolism. For example:

- Intravenous diazepam can produce obtundation and hypotension in patients with hepatic decompensation or advanced cardiopulmonary disease (11).
- Intravenous lidocaine can cause confusion, agitation, dysarthria, or hallucinations at a standard infusion rate (2 mg/min) in patients with liver disease, heart failure, or concomitant administration of propranolol (12).

Drugs that normally undergo substantial metabolism in the "first pass" are likely to accumulate and produce signs of drug toxicity when given at usual therapeutic doses to patients with cirrhosis.

- Enhanced bioavailability and decreased clearance has been demonstrated in cirrhotic patients for analgesics such as pethidine, pentazocine, and salicylamide (13).

Drugs with the highest hepatic clearances had the largest increases in bioavailability in patients with cirrhosis, probably due to portosystemic shunting.

Heart Disease. Patients with heart failure (and congestion of hepatic blood flow) are as vulnerable as those with hepatic disease when it comes to clearing drugs that require hepatic metabolism.

- Theophylline has a prolonged serum half-life in patients with acute cardiogenic pulmonary edema (mean, 23 h) compared to normal controls (mean, 7 h) (14).

Although most of the heart-failure patients in this study were over 65 years of age, little effect of age was found on the serum half-life among normal subjects (who varied widely in age). The authors speculate that the decreased clearance of theophylline in patients with heart failure was due to a combination of altered liver enzyme function and reduced hepatic blood flow.

Sometimes "cardiotoxic" events are attributed to a drug when they are more likely to be due to the underlying heart disease that is being treated. Early reports of the use of intravenous phenytoin claimed that most drug-induced fatalities occurred in elderly patients with cardiac arythmias. The doses used in these earlier studies (100–250 mg) were much lower than those subsequently shown to be safe in both old and young seizure patients (1000–1500 mg).

- Elderly seizure patients have an increased incidence of phenytoin-induced hypotension, but no serious cardiotoxicity (15).

This report concluded that serious arrhythmias were more likely to be a function of underlying cardiac disease than an effect of phenytoin itself.

Drug–Drug Interactions

Patients who develop ADRs are more likely to be taking six or more drugs than those who do not experience ADRs (6). The influence of the ingestion of multiple drugs on the potential for drug–drug interactions was examined by Brown and others (16) in two homes for the elderly. They found that the patients at highest risk for developing interactions were prescribed twice as many routine drugs and three times as many "as needed" agents as patients at lesser risk. The most commonly identified combination likely to result in a drug–drug interaction was

- a digitalis preparation with a diuretic

Tesh and colleagues (17) examined charts of 840 patients in two medical wards and one surgical ward of a British teaching hospital and found 38 prescriptions for potentially interacting drug combinations. Some of the most common included

- tetracycline/iron or antacids—reduced absorption of tetracycline
- cephaloridine/furosemide—nephrotoxicity
- gentamycin/ethacrinic acid—ototoxicity

Note that these reactions were "potential" only, not real ADRs.

More recently, Gosney and Tallis (18) inspected charts of 573 elderly patients admitted to either general medical or geriatric wards of a teaching hospital and found 133 prescriptions for potentially interacting drug combinations. Some of the most significant pairs were furosemide/aminoglycoside (ototoxicity, nephrotoxicity), furosemide/cephalosporin (nephrotoxicity) and furosemide/prednisolone (hypokalemia). Most all of these potential interactions could have been prevented by choosing alternate drugs or by supplementation (with potassium, for example).

Influence of Age on Pharmacokinetics

The pharmacokinetics of many drugs are altered as a function of age (19, 20). Drug absorption is only occassionally affected, usually by a reduction in the rate of gastric emptying. Other aspects of kinetics, such as drug distribution, metabolism, and renal clearance, change in many individuals with increasing age.

Drug Distribution. Older people tend to have more body fat and less muscle mass than younger individuals. Williamson and others (21) reported that 37% of elderly women who were followed up in outpatient practices were moderately to grossly obese, compared to 21% of elderly men. This sex difference in body fat content may account for the kinetic differences that Greenblatt and others (22) observed when they studied the distribution and clearance of diazepam in the elderly. The serum elimination half-life of this drug had been shown earlier by Klotz and others (23) to increase linearly as a function of age. Their Veteran's Administration study population, however, was composed primarily of men. Greenblatt's group found the increased half-life of diazepam in elderly women to be largely explained by larger volumes of distribution (diazepam is a fat-soluble drug). In elderly men, the increased half-life was primarily the result of decreased hepatic clearance.

Metabolism. Drugs that normally undergo substantial metabolism in the "first pass" are likely to accumulate in the elderly, although the age-related changes are less dramatic than those caused by heart failure or cirrhosis. For example:

- Clearance of propranolol declines with age, probably due to changes in hepatic blood flow (24, 25).

Schmucker (20) states that, on the average, there is a 30–40% drop in splanchnic blood flow in the elderly. In spite of this, elderly patients do not seem to be more sensitive than the young to beta-blockers. The most feasible explanation for this apparent paradox is that there is a concomitant decline in the sensitivity of beta-receptors to both agonists and antagonists with increasing age (26).

Renal Clearance. One review of the influence of age on pharmacokinetics, citing cross-sectional data, states that there is a decline in renal function with age (20). A recent longitudinal study, however, has shown that as many as one-third of the general population experiences no decline in creatinine clearance as a function of age (27). Nevertheless, drugs such as

- amantadine–cleared by renal tubular secretion

have serum elimination half-lives in the elderly that are double the half-lives in the young (28). Therefore, doses of this antiparkinsonian (and antiviral) agent given to older persons need to be adjusted accordingly.

Influence of Age on Pharmacodynamics

Some drugs produce more exaggerated effects in the elderly than in the young, not because of changes in kinetics, but because of changes in the way the drugs interact with their effector organs (29).

Warfarin. Warfarin has been shown to produce a greater degree of anticoagulation in the elderly than in the young, in spite of the fact that older patients are usually maintained on lower doses (30). Shepherd and others (31) could find no age-related changes in warfarin clearance, volume of distribution, or protein binding in either humans or rats. These authors did, however, see a much greater inhibition of clotting factor synthesis in the elderly than in the young at any given plasma warfarin concentration.

Neuroleptics. The neuroleptics are known to cause hyperkinetic involuntary movements of the oral-buccal-lingual area with long-term use. Tardive dyskinesia (TD) is thought to have a higher incidence in the elderly than in the young. Thirteen of 20 studies that have examined this issue have shown a significant relationship between age and the prevalence of TD (32). DeVeaugh-Geiss (33) recently described 42 schizophrenic patients who were followed up in a TD clinic (ages ranged from 22 to 73 years). He withdrew antipsychotic medications from as many patients as possible (60% of patients discontinued all neuroleptics). Complete remission of TD was seen in 14% and partial remission in 33%. Older patients were less likely to experience remission or improvement than younger ones. This study suggests that the relationship between age and the prevalence of TD may have more to do with TD remission following discontinuation of drug therapy than with the incidence of TD.

Tricyclics. Tricyclic antidepressants (TCAs) are known to cause delirium, largely because of their anticholinergic activity. Most authors agree that older patients are more vulnerable to this ADR, although they disagree about the incidence. Davies and coworkers (34) reported that 35% of TCA-treated patients who were over 40 years of age suffered confusional episodes, compared to 1% of those aged under 40 years. Meyers and Mei-Tal (35) and Danielczyk (36) found much lower incidences of delirium in their TCA-treated elderly populations (7% and 5%, respectively).

One interpretation of the disparity of these findings is that elderly psychotic patients may be more vulnerable to this ADR than elderly depressed patients (55% of Davies' subjects were either schizophrenic or psychotically depressed; 47% of Meyers' subjects had major depression without psychosis). Blood levels of TCAs were not necessarily higher in the elderly patients in these studies. This was consistent with the earlier findings of Ziegler and Biggs (37), who failed to demonstrate a correlation between TCA blood levels and age.

Methods for Avoiding ADRs

The report of the Royal College of Physicians (38) attributed the increased incidence of ADRs in the elderly to a variety of causes: (a) inadequate clinical assessment, (b) excessive prescribing, (c) inadequate supervision of long-term medication, (d) altered pharmacokinetics and pharmacodynamics, and (e) poor compliance. Several methods should be employed to minimize ADRs.

Make Accurate Clinical Assessments. A good example of inadequate clinical assessment is the pattern of psychotropic drug use in the elderly. Achong and others (39) found that 82 of 1,431 chronically ill elderly outpatients were significantly depressed, but only one was being treated with a TCA (14 were treated with anxiolytics and 8 received antipsychotic agents). Of the 64 with serious anxiety, only 15 were being treated with anxiolytics (13 were treated with antipsychotic drugs). More accurate behavioral evaluations should reduce the incidence of TD, since neuroleptics are rarely the drug of choice for the treatment of depression or anxiety, the two most common behavioral disturbances in the elderly.

Minimize Total Number of Drugs. Twice as many medications as the national average were prescribed for the elderly in Great Britain in 1980 (38). Many physicians would argue that this pattern is appropriate, since elderly persons in Britain have, on average, three disabilities or more (21). Analgesics, cardiovascular agents, and diuretics are the drugs most commonly prescribed for elderly persons, appropriately reflecting the high incidence of arthritis, hypertension, and heart disease in this age group (40–42). Taking a careful drug history during each outpatient visit or hospital admission is one way of avoiding excessive prescribing, because physicians are reportedly unaware of 21% of the medications their patients are taking (43).

Monitor Long-Term Medications. In order to prevent TD in psychotic elderly patients, the lowest effective dose of neuroleptic should be prescribed in as short a course as possible. Signs of TD should be elicited at each outpatient visit, so that the drug can be tapered or discontinued when the first signs of TD appear (the longer this ADR exists, the more likely it is to be irreversible).

A similar approach can be used to prevent drug-induced ("on-off") motor fluctuations in Parkinson's disease (PD). DeJong and others (44) showed that PD patients whose levodopa regimen was initiated too early or maintained at high doses too long were the patients most likely to develop variations in response. PD patients should be questioned about the incidence and severity of "on-off" symptoms at every office visit. They should be maintained on as low a dose of levodopa as possible, and the levodopa regimen should be supplemented with bromocriptine to optimize therapeutic response (45).

Start with Low Doses. Because there are age-related changes in the pharmacokinetics and pharmacodynamics of so many drugs, it is prudent to start with lower than the usual therapeutic dose of any drug given to an elderly patient. The dose can be titrated up slowly so as to prevent the ADRs that most patients eventually develop tolerance to (sedation with tricyclics; dizziness with phenytoin; nausea with levodopa).

Give Written Instructions. The most common difficulties in achieving compliance among elderly outpatients are that these patients often omit prescribed medications and have inaccurate knowledge of the purpose of their prescribed medications (46, 47). Nurse-supervised teaching programs for in-patients have been shown to correct simple errors that patients make in self-medication and to identify patients who need assistance with their dosing (48). Wandless and Davie (49) have shown that tear-off calendars are more effective than tablet identification cards for improving drug compliance among elderly outpatients. Either one of these methods of giving written instructions, however, is preferable to giving none at all.

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Surveillance for Colonic Polyps

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Campaigns to detect colon polyps in asymptomatic people seem to me at present to represent a triumph of faith over fact. In the following somewhat biased discussion I comment upon (a) detection and screening, (b) removal of colonic polyps and adenomas, and finally (c) recommended follow-up programs.

What Good Does Surveillance Do?

The picture on the front page of *The New York Times* in January 1985 of the President of the United States on his way to colonoscopic examination appeared in space usually reserved for matters of state or national finance and exemplified the attention being given to surveillance for colonic tumors.

Let us accept the definition of screening as the process of detecting disease at an asymptomatic stage in the general population (1). Patients with symptoms, like the President, and persons from "cancer families" require entirely different considerations, which I do not discuss in what follows.

The fundamental assumptions on which surveillance for colonic polyps is based are (a) adenomas become cancers; (b) the outlook for colon cancer has not materially improved by early diagnosis and treatment; (c) surveillance of asymptomatic people will lead to earlier detection and therefore to a better outcome; and (d) consequently, the general population should be urged to undergo screening by Hemoccult, sigmoidoscope or colonoscope, air-contrast barium enema, and—one may predict—someday by such newly found bowel-cancer genes as those on chromosome 5.

Yet the 1978 consensus conference, the last to scrutinize the matter in public, concluded that no data showed that screening by fecal occult blood test reduced mortality in the screened population; accordingly, mass screening programs were not then recommended, because the benefits of screening, still unknown, were likely to be limited to people aged over 40 years or to those at high risk because of other disease or a strong family history. It was stipulated that only a clean colon should be examined, whether by air-contrast barium enema or endoscopically. (In 1988, I believe, the colonoscope would be the preferred choice.) The American Cancer Society went further in recommending an annual rectal examination for people over 40 years old and—for people over 50—an annual Hemoccult study, and sigmoidoscopy every three to five years after two initial examinations one year apart were negative (2). Spurred by the hope that some action will achieve something good later, such recommendations come in the spirit of other goodhearted agencies' proclamations of firm recommendations for massive changes in American dietary habits to reduce heart disease—or colon cancer.

Testing the Stool for Blood. Although three current methods are available, in the form of the guaiac, the immunochemical, and the fluorescent (Hemoquant) test, the most generally available is the guaiac, largely in the form of Hemoccult II. Simon has provided its authoritative assessment (3). We cannot reasonably accept tests other than the Hemoccult as equivalent to Hemoccult without some objective assessment; indeed, apparent variations in the batches of guaiac account for different results with Hemoccult I and Hemoccult II, the latter now the standard. The sensitivity of guaiac varies because its natural source varies and therefore each "batch" needs standardization. That aside, lower gastrointestinal tract bleeding is more likely than bleeding

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in the upper tract to yield a positive test because hemoglobin in its passage through the gut is altered by bacteria and enzymes that destroy the peroxidases responsible for oxidizing guaiac to a blue phenol.

In health only about two ml of blood is lost in the stool each day, larger amounts usually indicating some breach in the digestive tract. The Hemoccult test remains negative with passage of 5–10 ml of blood, but 80%–90% of tests will be positive when more than 20 ml is passed in the stool.

Such numbers remain arbitrary, because many other factors affect results: a diarrheal stool will be diluted with water, to a lower hemoglobin concentration, whereas rapid passage will preserve the important peroxidases. Generally, Hemoccult slides should *not* be rehydrated because that increases the percentage of positive results to reduce the positive predictive value, the likelihood that a lesion will be detected when the Hemoccult is positive. Dietary restrictions turn out to be arbitrary as well as confusing; Simon assures us that it makes sense to investigate any positive test in persons taking a regular diet if the stool cards have not been rehydrated. Iron and aspirin increase the amount of blood in the stool, and vitamin C inhibits the chemical reaction, so that these three common medications should be avoided if possible when stools are being tested. Even so, it is prudent to investigate sources in such patients.

In my own practice, when I check the stools for blood in asymptomatic patients, I use Hemoccult II slides in patients on a regular diet, and my choice is usually to test five slides. If these are positive, and no source is obvious in the patient's story, I investigate further, usually at least by colonoscope; cost-benefit analysis, the abandonment of barium studies by the young generation of radiologists, and other considerations not pertinent here have convinced me that the colonoscope is the first and best examination to carry out when stools are positive for blood in the asymptomatic patient undergoing screening. I always ask about aspirin intake, for it is surprising nowadays how many people take aspirin for pain or health.

I usually say that 80% of colonic polyps do not bleed and that 80% of cancers do, but I do not know how true that is. Presumably bigger polyps bleed more than little ones, but I have no idea whether a microscopic cancer will bleed more than a microscopic adenoma (4). I do know that having a stalk lets a polyp twist in the colon to increase vascular congestion and bleeding (5).

A major problem in assessing the utility of such an approach is that conclusions about false positivity or negativity depend upon how far the physician has gone to ascertain the source of blood loss. For example, when we talk about a "false positive" Hemoccult, do we imply that investigation was so thorough that enteroclysis and assessment of platelet function has been carried out, or do we simply mean that a colonoscopic examination proved negative? It is so difficult to tell what is known about the results of Hemoccult screening that a simple conclusion about whether a colon tumor was found might be all that was needed.

Indeed, from a practical clinical standpoint, carrying out only a colonoscopic test in the asymptomatic person might be a sufficient response to finding blood in his stool. Although such an approach might miss an occasional important lesion in the stomach and a rare one in the small intestine, it could be justified, given the little that can be done for gastric malignancy, the rarity of tumors in the small bowel, and the usual futility of treating other lesions which have not yet caused any symptoms. Medicolegal considerations, however, usually move the physician to more intrusive maneuvers.

Proffered reports about large-scale studies of Hemoccult testing followed by endoscopic examination now underway—these reports are confessedly premature—suggest that when allegedly asymptomatic people are surveyed, cancers are found at an earlier stage than usual; that is, there are more than the usual number of Dukes A or B lesions than would be the case in patients studied because of obvious bleeding or abdominal pain (6, 7). One problem, of course, is whether people who volunteer to undergo screening studies have, in fact, some suspicion that something is going on, and whether that leads to "selection bias." Whether screening people of similar age whose Hemoccult tests are negative would yield similar numbers of early colon cancers has not yet been reported. Such control studies are essential if the place of surveillance programs is to be properly assessed. The costs of such studies vary; a recent estimate was that the discovery of each new colon cancer cost $9,670 (8).

Sigmoidoscope Screening. Screening by sigmoidoscope, which almost everyone now agrees should be of the fiberoptic variety, has two aims: (a) to find cancer which has already developed, and (b) to remove polyps which may later become cancerous. Sigmoidoscope surveillance depends on faith in the adenoma-to-cancer sequence and the validity of reported studies. Costs for such an approach are mounting, the benefits for people who are neither symptomatic nor predisposed remain unproven, and the supporting data to prove contentions will not be available until at least 1992. Fortunately, the hazards of sigmoidoscopic screening to the individual patient are quite small.

That a benign adenoma becomes a cancer used to be denied, but observations by Morson and others in the 1960s and 70s led to a general conviction that adenomas do become cancers and that remnants of a previous adenoma can still be found in some cancers. Although it is hard to find anyone who holds to the old faith that declares once-an-adenoma-always-an-adenoma, the impossibility of removing a polyp to show that it is benign and then following its "natural" history is self-evident. An exception may be a study of the natural history of untreated colonic polyps from the Mayo Clinic: a retrospective analysis of 226 patients whose colonic polyps were followed up in x-ray studies for over 5 years yielded a reported cumulative risk of a cancer at that same site of 2.5% at 5 years, 8% at 10 years, and 24% at 20 years (10). The possibility that cancer had always existed at the site was recognized, but to the study authors it seemed likely that the outcome supported the adenoma-to-cancer contention. At the least, the reported cumulative risk suggests what the natural history of "polyps" is (in this case, "polyps" seen on x-ray and not removed).

Doubting Thomases are assured that when all adenomas have been removed in a search-and-destroy operation, some decades later the number of colon cancer cases will have declined in those so cleansed, in contrast to a steady rate of colon cancer in a control population whose adenomas have not been searched out until they caused symptoms. Yet convincing evidence is not yet in. It is evident that the more people who are sigmoidoscoped, the more polyps are found, and that in older people even more polyps will be found (8). Sigmoidoscopic examination detects far more polyps than Hemoccult studies, and the fiberoptic sigmoidoscope finds more than the rigid sigmoidoscope simply because flexible instruments penetrate deeper into the colon.

Generalizations can be offered, with the proviso that general policy may not be prudent for the patient in front of you. That is, physicians may agree that a certain number of negative Hemoccult tests reduces the possibility of colon cancer in someone without symptoms, but the patient who comes to see his physician because a neighbor has just died with colon cancer can be reassured truthfully only by colonoscopic study. Although cancers found in the colon on such screening are at an "earlier" stage than those which cause symptoms, the many biases inherent in such studies suggest skepticism. For example, whether such patients have a longer life-span, or whether "lead time" bias is operating, has not yet emerged; the diagnosis may simply have been made earlier, and survival not prolonged. Studies from Kaiser (11) have suggested not only that polyps are found more often in patients who are screened than in those who are not, but—more important—that fewer screened patients than nonscreened controls had died from colon cancer five years later. Unfortunately, overall mortality was the same in the study group and in the control group. The large studies from Minnesota and New York based first on Hemoccult screening are not scheduled to report results until 1992.

Treatment for Colonic Polyps

Once a polyp is found, what should be done? The finding of a colonic polyp mandates a colonoscopic test to look for others, as the first step. Regardless, it seems clear that a polyp smaller than 1 cm may be fulgurated without biopsy with no significant subsequent risk of cancer at that site, according to Mayo Clinic statistics (12). Such small tumors, it is now universally agreed, have such an extraordinarily small likelihood of being a cancer, on the order of less than one percent, that they can be destroyed without biopsy; on follow-up such patients prove no more likely to have another polyp than the general population.

Are Hyperplastic Polyps "Stool Pigeons"? On the other hand, not only are polyps larger than 1 cm more likely to prove cancerous the bigger they are, but they are more likely to be followed by a subsequent cancer, although not at the site of the original polyp: in the Mayo Clinic study, patients with adenomas larger than 1 cm ran an increased risk of subsequent cancer in the colon about three times that of the general population. Whether a hyperplastic polyp is the same kind of "stool pigeon" as an adenoma, pointing to other polyps in the bowel, is under debate.

This raises a perplexing question. If the attempt in surveillance studies is to show a decreased incidence of subsequent colon cancer by removing adenomas, then the task may be sisyphean: the propensity for new cancers may so overwhelm any benefit from adenomas expunged that it may not be possible ever to demonstrate a decrease in colon cancer prevalence. Outcome in terms of total morbidity may be the only important criterion. For that, adequate control groups will be necessary.

Currently, then, it seems reasonable to conclude that a polyp smaller than 1 cm can safely be fulgurated, but that polyps larger than 1 cm should be removed and studied. In either case, follow-up is important, and the colonoscope is the instrument that should be used.

Once an adenoma is found, total scrutiny of the colon is in order, to look for other polyps or cancer; the increasing prevalence of right-sided colon cancers underlines the importance of this maneuver (13).

Follow-Up

How frequently should colonoscopic study be repeated in such patients? The answer to that question too has been argued. Studies from Erlangen (14) of adenomas larger than 5 ml suggest that once a colon is free of polyps, 1.5% of patients will develop another polyp at the end of a year, and 8.9% will develop another polyp at the end of five years: a four-year follow-up for patients with only one colonic adenoma is suggested. In contrast, patients with multiple adenomas from the beginning are likely to have new polyps at one year at a 2.7% frequency, and the figure rises to 29.4% at five years; for such patients a routine two-year follow-up seems reasonable. These intervals are more dilatory than those usually suggested in the United States.

Obviously such numerical recommendations can be generated in wide variety, but for individual patients, decisions are not as easy. I conclude that the frequency of follow-up after a single adenoma is found should be one year, to reassure patient and physician alike that no other lesions were missed at the first colonoscopy, and that thereafter—as a matter of policy— the follow-up should be every three years.

For patients with multiple adenomas discovered for the first time, colonoscopic study every year for a few years is in order, but I am not sure of appropriate recommendations beyond that time. Many physicians repeat colonoscopy in such patients at yearly intervals, apparently forever. I am concerned that studies may have grouped together patients with a "sporadic" polyp and no predisposing family history with those who should undergo more frequent surveillance, but I know of no way at present to tell.

In any event, what still needs to be shown is that screening the colon of asymptomatic patients (a) identifies very early cancers in a higher-than-expected frequency; (b) lets such patients live longer than controls; and (c) decreases the subsequent frequency of colon cancer.

How to Treat the Polyp Containing Cancer

There seems to be almost universal agreement that a polyp on a stalk, even one containing cancer, can safely be removed without subsequent resection of the colon if the cancer has "good" histology, which means that it has not spread below the submucosa, is well-differentiated, and has a stalk (15). Claims should be reviewed in this regard, but a tumor confined above the submucosa is so unlikely to have metastasized as to make the risk of a "prophylactic" colonic resection greater than any subsequent risk of cancer at that site (16–18).

Adenomas with the "unfavorable" characteristics of poor differentiation or invasion, or involvement of lymphatics, require resection. The clinician should review the specimen and the interpretation *in person* with the pathologist, to avoid misunderstandings. Although such assessment seems easy in theory, pathologists point out that it is far easier to assess these criteria in a polyp lying in a segment of colon already resected than it is when a polyp with a stalk has been removed at colonoscopy, and relationships are less clear.

Still, the result of follow-up studies from both medical and surgical observers are reassuring about this prudent approach. Putting together the results of eleven studies reported through 1986, Cranley (19) found an overall 8.9% chance of a later cancer in patients with a pedunculated polyp; the risk dropped to 0.3% in polyps with "good" histology. For sessile polyps, the chances of a later cancer were far higher—19.3%; with "good" histology, however, the likelihood was only 4.8%.

In a combined review of malignant polyps with invasion below the muscularis but with clear margins, Wilcox (20) assessed the chances of residual disease at 10%, but emphasized the disparity in different studies. Supporting views include those of Fucini and co-workers, who point out (21) that when resection for such lesions was carried out, no lymph nodes involved with cancer were found, but that the reported incidence may vary from 3% to 10%. Colacchio, however, in a study much criticized for its criteria, claimed lymph-node involvement as high as 25% (22).

In such retrospective studies, however, we can never be certain why a certain procedure, resection or follow-up, was preferred. Still, at present I conclude that the experts are right, or at least prudent: a pedunculated polyp with a "good" histology, even with cancer in it, warrants follow-up and not resection of the colon. Endoscopic follow-up of such patient should be at 3–6 months for polyps with good histology and cancer. Sessile polyps, on the other hand, still deserve resection when they contain cancer, even if the histology is "good."

Conclusions

Let me reemphasize that such conclusions are temporary, and subject to change without notice. I would reserve Hemoccult screening for asymptomatic persons without predisposing features until the figures from national trials are in. I do Hemoccult screening of patients with pain or those whose symptoms are of uncertain origin, in order to ascertain who deserves more intensive studies. I would advise sigmoidoscopic study only for those with predisposing features, that is, people with first-degree relatives who have had a colon cancer and members of a "cancer family" (23), those who have been found before to have an adenoma, particularly one larger than 1 cm in size, and those with such predisposing diseases as inflammatory bowel disease. Many of the patients in these groups will deserve colonoscopic study. I can understand the zeal of clinicians who routinely sigmoidoscope all their patients over a certain age. But I would certainly include in the group to undergo regular screening other patients, those with irritable bowel syndrome or diverticular disease standing out simply because their chronic symptoms may mask the development of a tumor. But in this uncertain world I would settle for clinicians investigating thoroughly, with colonoscopy, all their patients with newly developed colonic symptoms or rectal bleeding.

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General Article

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Assessing the Effects of a Strike on Nursing Home Patients

Richard R. Neufeld, M.D., Joseph Maiorca, PhD, Manuel M. Rodstein, M.D., and Joel Gross, M.D.

Abstract

To assess the effects of a strike by ancillary employees on nursing home residents, a questionnaire designed to evaluate state of emotional health and degree of satisfaction with delivery of services was utilized. Responses to the questionnaire were collected from 24 mentally competent patients at the onset of the strike, on two separate occasions during the strike, and two months after the strike had ended. Additionally, to evaluate indices of clinical care, analysis was made of resident mortality, the occurrence of fractures, transfers, and discharges, and the number of laboratory procedures obtained for periods before, during, and after the strike. No significant deterioration of emotional health or of satisfaction with services occurred among the mentally competent residents who were interviewed. Indices of clinical care remained equal to prestrike levels. Although some bias may have been introduced by the collection of responses by physicians involved in caring for the patients, the efforts of committed staff members and temporary workers appeared able to reassure patients and to maintain the provision of adequate services.

There is little in the literature documenting the effect of strikes by health-care employees on patient care or how the patient perceives or evaluates the experience. A survey of a six-week closure of an active British day hospital for the elderly (1) revealed that the short-term effect on patients' physical and mental state was marginal. However, as the closure continued, those patients without adequate auxilliary services deteriorated in mobility, personal hygiene, and mental status. In a study evaluating hospital services during a strike of nonmedical and nonnursing employees, patients were less satisfied only with housekeeping and delivery of dietary-food service during the strike (2). The results of the questionnaire used by these authors revealed that the medical and nursing care remained equal to or above prestrike levels.

A labor crisis involving nursing home personnel may have deleterious effects upon patients. Not only are elderly nursing home residents physically disabled, but an increased proportion is being admitted with various cognitive and psychiatric disorders (3, 4). The objective evaluation of nursing home patients' satisfaction with delivery of services as well as of their emotional health during a period of labor strike is a difficult undertaking. Nursing home care, to a greater degree than hospital care, relies heavily on the long-term commitment and compassion of nontechnical staff. The changes produced by interpersonal losses and environmental stresses during a strike have the potential to change an elderly person's susceptibility to physical and emotional illness (5–8).

The purpose of the present study was to assess the quality of care and services rendered to long-term care residents during a prolonged labor dispute. To evaluate the effects of the job action on patient care, the responses of 24 mentally competent patients to a questionnaire which

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notes state of emotional health and satisfaction with delivery of services were collected at the beginning of and during and after the job action. In addition, in order to assess the level of care of cognitively impaired residents, an institutional analysis was made of monthly laboratory procedures, number of rehabilitation visits, deaths, and transfer to hospitals at periods before, during, and after the strike.

Description of the Strike. From July 16 to August 28, 1984, a job action took place in a 514-bed nursing home facility with 476 resident patients in skilled-nursing-facility floors and 38 resident patients in intermediate-care floors. The action involved 475 union employees consisting of nursing aides, orderlies, and workers in housekeeping, dietary, laundry, and maintenance services. Care of the resident patients was rendered by licensed nurses, nonnursing staff employees, volunteers, and temporary helpers, many of whom worked extended shifts. The ratio of registered nurses to nursing home patients generally remained equal to or slightly greater than prestrike levels; the number of auxilliary floor staff diminished slightly.

During the first few weeks of the strike only essential patient care services were carried out, and no new admissions were scheduled. Patients were transferred only if they required hospitalization, and during the early phase of the strike only one patient from a skilled-nursing-facility floor was sent to live with friends or relatives.

Patients, Materials, and Methods

The Survey Instrument. The 27-item questionnaire consisted of a 15-item "satisfaction domain" and a 12-question "affective domain" which were developed specifically for assessing nursing home care (9). Each of the 15 items on satisfaction is a statement read aloud by the interviewer to the study participant, who is asked to agree or disagree. Frequency of satisfaction was scored on a descending scale of 6 to 0 ("most of the time," 6; "some of the time," 3; "little of the time," 1; "none of the time," 0). For negative items the scoring was reversed.

The affective domain contained 12 questions (Table 1). The participant was asked how often during the past several weeks he or she had felt a particular emotion. Factor analysis demonstrated that the affective questions were divided into either positive or negative emotions (9). The scoring was identical to that of the satisfaction domain.

This instrument has been used successfully in a nursing home population, and test-retest reliability and validity coefficients have proved to be psychometrically sound (9).

Subjects. Twenty-four verbally consenting mentally competent resident patients were randomly selected for the study. Fourteen resident patients were selected from the intermediate-care floor (HRF) and ten residents from two skilled-nursing-facility (SNF) floors. The residents were selected from floors which had the closest proximity to the picket lines and exposure to demonstrations on the street. Charts were reviewed to verify mental competence. Three-fourths of the study participants were women (Table 2).

On day one of the strike, alert residents on three floors were randomly interviewed by physicians and asked to voluntarily participate in the study.

The same residents were interviewed during weeks three to four of the dispute and later at weeks five to six. The majority of the residents were interviewed by the same interviewer. The strike was finally settled after 42 days. Eight to nine weeks after resolution of the strike, the same residents were again interviewed. Four intervals—day one of the strike, weeks three to four, weeks five to six, and weeks eight to nine, were used in analysis of questionnaire responses.

To assess the care given to mentally incompetent residents, an analysis was made of admissions, transfers, discharges, and deaths. Such laboratory procedures as total number of cultures and total number of laboratory procedures were recorded for periods before, during, and after the strike. The number of patients with new fractures occurring during the strike was noted, because this is an objective, easily measurable finding.

Results

Satisfaction Scores. Analysis of mean satisfaction scores (Table 3) by sex at the four time intervals revealed a significant sex difference ($t = 3.61$, $p < .01$) at week 5–6 (Table 4). Men during this interval tended to have less favorable satisfaction scores. Analysis of the six men in the study revealed that four were from the skilled-nursing-facility population, and three of them were wheelchair-dependent and perhaps more debilitated and demanding than other participants.

Analysis of responses on the satisfaction scale (Table 4) yielded a nonsignificant difference

TABLE 1

Central House Strike Questionnaire

Resident ____________ UNIT ____________ TIME ____________
Interviewer ____________ Date ____________

Satisfaction Domain	MOST of the time	SOME of the time	LITTLE of the time	NONE of the time	Affective Domain	MOST of the time	SOME of the time	LITTLE of the time	NONE of the time
Staff shows a personal interest					Bothered by nerves				
Something done about complaints					Anxious				
Overall satisfaction					Happy				
Nursing staff cares about you					Life is interesting				
Help comes within a reasonable time					Wake up fresh and rested				
This is a cheerful place					Cheerful				
Can keep personal possessions					Felt lonely				
Life is boring here					Feel sad				
The food is good					Something to look forward to				
See doctor when needed					Depressed				
Room and surroundings are clean					Worried				
Have enough privacy					Thought about suicide				
Choice of bedtime									
Personal belongings have disappeared									
Amount of noise bothers you									

Adapted from Kane et al., 1983, 388 (9).

between the SNF and HRF samples with respect to attitudes toward delivery of services. Despite the statistical nonsignificance, the SNF sample showed at week 5–6 a trend toward a less favorable attitude than the HRF sample delivery of services. After the resolution of the strike, in week 8–9, this tendency toward less satisfaction resolved. Although the SNF sample had a less favorable attitude toward delivery of services during the third interview, there was no significant difference between the SNF and HRF samples with respect to the emotional scale at any time interval. Overall, the data indicate that the nursing home residents reported little appreciable change in emotional well-being and minimal dissatisfaction with delivery of services during and after the labor dispute.

Laboratory Procedures. Analysis of monthly laboratory procedures during a prestrike (June), a strike (August), and a poststrike (September) period showed that the total number of cultures (urine, stool, blood, sputum, skin, and decubitus ulcer), blood tests, and urine analyses was greatest during the strike period (Table 5). However, the percentage of positive cultures for August (40%) was only slightly above the average

TABLE 2
Characteristics of Sample Surveyed (24 Patients)

Sex		**Country of birth**	
Male, no. (%)	6 (25%)	U.S., no. (%)	15 (62%)
Female, no. (%)	18 (75%)	Other, no. (%)	9 (38%)
Age		**Category of nursing care**	
Mean ± SD, years	84.8 ± 7.3	HRF	14 (58%)
Median, years	84.7	SNF	10 (42%)
Range, years	71–99		

HRF, intermediate-care faculty; SNF, skilled-nursing-facility.

for the three months, and equal to the percentage in September. The increase in total cultures and blood chemical and urine analyses probably reflects greater surveillance during the strike period, as well as maintenance of sicker patients in the institution for a longer period of time.

The total deaths, including the number of deaths occurring at the nursing home, was 8, and the number of our patients who died while hospitalized outside the nursing home (2) was no greater for the month of August than any other month. There were 17 new admissions and 16 patient transfers to hospitals in the month of August, each number slightly above average, because there were no new admissions and very few transfers to outside hospitals during the first two weeks of the strike (July 16–30). By August the total number of physical therapy treatments was 1,232; of speech pathology treatments, 29; and of occupational therapy treatments, 539. These totals represented a return to normal routines. The total number of fractures in August was 5; in July the number was 7, slightly above the monthly average of 4.5, but equal to the number in May, a prestrike month.

TABLE 3
Strike Questionnaire: Means and Standard Deviations (N = 24)

	Mean ± SD
Satisfaction domain (15 items)	
Day 1	51.8 ± 4.5
Wk 3–4	51.5 ± 6.0
Wk 5–6*	49.1 ± 7.6
Wk 8–9 (poststrike)	52.5 ± 4.7
Affective domain (12 items)	
Day 1	35.4 ± 9.1
Wk 3–4	35.9 ± 7.3
Wk 5–6*	33.6 ± 8.7
Wk 8–9 (poststrike)	35.5 ± 6.8

* N = 22; two residents—one who was febrile and confused, and another with transient ischemic attack—were not interviewed. Both were from SNF population.

TABLE 4
Mean Satisfaction Scores by Sex, Level of Nursing Care, and Strike Time Interval

	Strike time interval†			
	Day 1	Wk 3–4	Wk 5–6	Wk 8–9
Sex				
Female	69.5	69.33	70.18*	68.95
Male	67	63.83	47.16*	73
Level of nursing care‡				
HRF	48.43	48.88	48.47	46.61
SNF	48.37	47.56	43.07	46.47

* Significant ($t = 3.61, p < .01$).

† Not significant.

‡ Neither of the two level-of-nursing-care populations (HRF, intermediate-care; SNF, skilled-nursing-facility) were statistically significantly different in mean satisfaction scores at any time interval.

Discussion

The data indicate that the strike had little or no effect on participant's emotional health or satisfaction with services. Age and country of origin were not significantly related to either emotional health or satisfaction. However, when participants were compared by sex, the male resident patients, who as a group had a high proportion of functional impairment, were less satisfied with overall services, especially toward the latter part of the strike; the sex difference was significant at week 5–6. Three of six male participants were wheelchair-bound, and a fourth SNF male patient had significant functional impairment and thus made greater demands upon staff. It is likely that toward the end of the strike the staff on these floors became strained and burdened.

As a group the participants showed no significant changes at any interval on either the affec-

TABLE 5
Total Number of Institutional Laboratory Procedures by Month (Strike Period July 16–August 28)

	Bacteriologic cultures Total/no. (%) positive	EKG	Lab tests*
June	139/43 (31)	165	5535
Aug.	181/72 (40)	141	6500
Sept.	160/64 (40)	132	5328
Average	160/59.6 (37)	146	5787.7

* Blood chemistries and urine analyses. Each chemical analysis was counted individually.

tive or satisfaction-with-services scale. Surprisingly, neither the SNF nor the HRF residents as a group reported an increased frequency of negative emotions or dissatisfaction with services during the strike period. Although the male resident patients were less satisfied with services at week 5–6, this did not appear to affect their emotional well-being; they did not report an increased frequency of negative emotions.

These findings are in general similar to a study in a British day hospital during an industrial action (1). Although the British study found that "the ill-effects were not marked," a small minority of these homebound patients felt depressed, and several other patients deteriorated in personal hygiene and mobility.

Several committed staff members became so physically and emotionally exhausted that they needed to be sent home to rest. As a strike continues, a decline in services resulting from weariness of the staff is anticipated. Such a decline might be noticed first by functionally dependent residents who have the greatest need for services. As noted by Rosenberg et al. (2) during a hospital strike by similar personnel, some areas of services declined during the last third of the strike.

Analysis of laboratory data revealed that no deterioration in these services occurred. During the strike there was an increase in surveillance, resulting in more frequent cultures and blood tests. Since local hospitals were also on strike, an attempt was made initially to maintain sicker patients at the nursing home. Although no index of functional activities of daily living was monitored during the strike, the number of patient visits to physical, occupational, and speech therapy during the month of August was equal to prestrike levels. Although the number of fractures and deaths for the month of August was slightly above the average, it was not higher than numbers in some other nonstrike months.

Many factors contribute to the ability of a nursing home to respond and sustain adequate levels of care during a stressful strike (10, 11). The strike reported on here had been anticipated, and past strike experience had enabled planners to anticipate the primary needs of the residents and the institution. The nonstriking and temporary staff responded effectively and in a spirit of cooperation to the crisis. The spirit of cooperation allowed a sharing of responsibilities and burdens which reassured the residents.

As the strike continued and its outcome became less certain, workers became increasingly exhausted and desired to return to normal responsibilities. Flexibility and the ability to adopt new approaches waned as the strike was prolonged. Experimentation with long and short shifts, overlapping shifts, and drug holidays was not done. Although friends and families of the residents often volunteered their services, few were able to supervise and maintain the dependent and frail elderly person at home. It became clear that community support services to maintain patients at home were either lacking or too cumbersome to mobilize for a short and temporary crisis.

Our study demonstrated the feasibility of gathering data from an alert nursing home population by direct questionnaire. Those residents who were interviewed were more mentally alert and functionally more independent than the confused, disoriented, and bed-bound patients who occupy many of our nursing home beds. The fact that the questionnaire was administered by physicians who were caring for the patients in the nursing home during the strike may have introduced some bias, and conceivably affected the outcome of the questionnaire. However, only one question from the "satisfaction domain" referred directly to satisfaction with physician services. A significant bias is unlikely. Furthermore, clinical indices of patient care correlated with the emotional state and satisfaction with services as perceived by the residents. In this particular circumstance, patient care was not adversely affected by the strike.

As our population ages and additional nursing home beds are required, more health care workers will be needed. As these workers seek the benefits and security of unionization, the potential for both larger-scale strikes and disruptions of health care services to the aged becomes a greater possibility. The legitimate needs of the health care worker should be met without sacrificing the well-being of the debilitated elderly, whether in the community or in an institution. Perhaps an advisory council consisting of representatives of labor and management and an impartial health professional agreed upon by both parties should meet annually to update and to evaluate the needs, demands, and services of health care givers.

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3 Pharmacokinetic studies in patients with hepatorenal syndrome have not been done Part of the dose of nizatidine is metabolized in the liver In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine

Drug Interactions—No interactions have been observed between Axid and theophylline, chlordiazepoxide lorazepam, lidocaine, phenytoin and warfarin Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system therefore drug interactions mediated by inhibition of hepatic metabolism are not expected to occur In patients given very high doses (3 900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine 150 mg b i d was administered concurrently

Carcinogenesis, Mutagenesis, Impairment of Fertility A two year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa In a two year study in mice there was no evidence of a carcinogenic effect in male mice although hyperplastic nodules of the liver were increased in the high dose males compared to placebo Female mice given the high dose of Axid (2,000 mg/kg/day about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used The female mice were given a dose larger than the maximum tolerated dose as indicated by excessive (30%) weight decrement compared to concurrent controls and evidence of mild liver injury (transaminase elevations) The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats male mice and female mice (given up to 360 mg/kg/day about 60 times the human dose) and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect but, at a dose equivalent to 300 times the human dose treated rabbits had abortions, decreased number of live fetuses and depressed fetal weights On intravenous administration to pregnant New Zealand White rabbits nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus There are, however, no adequate and well-controlled studies in pregnant women It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers Nizatidine is secreted and concentrated in the milk of lactating rats Pups reared by treated lactating rats had depressed growth rates Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers

Pediatric Use—Safety and effectiveness in children have not been established

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups Age alone may not be an important factor in the disposition of nizatidine Elderly patients may have reduced renal function

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0 2%), urticaria (0 5% vs <0 01%) and somnolence (2 4% vs 1 3%) were significantly more common in the nizatidine group A variety of less common events was also reported it was not possible to determine whether these were caused by nizatidine

Axid® (nizatidine Lilly)

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU/L The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients All abnormalities were reversible after discontinuation of Axid

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo Rare reports of gynecomastia occurred

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients Rash and exfoliative dermatitis were also reported

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported

Overdosage: There is little clinical experience with overdosage of Axid in humans If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy Renal dialysis for four to six hours increased plasma clearance by approximately 84%

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea Single oral doses of 800 mg/kg in dogs and of 1 200 mg/kg in monkeys were not lethal Intravenous LD_{50} values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively PV 2091 AMP [041288]

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Obituary

Fenton Schaffner, MD
George Baehr Professor of Medicine
Chief, Division of Liver Disease
Mount Sinai
New York

Hans Popper MD, PhD 1903–1988

Hans Popper died on May 6, 1988 after a prolonged illness resulting from carcinoma of the pancreas. He was born in Vienna, Austria on November 24, 1903, the only son of Carl Popper, M.D. and his wife Emma. Thus began a long, fruitful life during which Hans was to make significant impacts on basic medical sciences, clinical medicine, and medical education. As a child he was exposed to the charm and graciousness of the city and country of his birth, which, before World War I, was dedicated to the good life. His father, a practicing physician, served as a role model and in 1922 Hans entered the University of Vienna as a medical student. Then as now, elective time in other institutions was permitted and Hans studied in Freiburg, Oxford, and Paris. After graduation he remained in the 1st Medical Clinic of the University of Vienna.

From his student days until his final illness Hans displayed a remarkable and insatiable curiosity about the function of the human body. He did research in the fields of biochemistry, dermatology, ophthalmology, nephrology, endocrinology, pathology, and hepatology. The list of publications that stemmed from this activity numbers almost 800 and it still continues to grow even after his death. An important theme running through most of these publications is the attempt to correlate structure and function in order to develop a dynamic approach to understanding the pathogenesis of diseases.

While still in Europe, Hans became interested in the liver. He left Austria in 1938 and came to Chicago as a research fellow in the Graduate School of the Cook County Hospital. He revived some of his earlier work on endogenous creatinine clearance and also began studying the distribution of vitamin A in the liver. This latter work earned him a Ph.D. in pathology from the University of Illinois in 1944. Two years earlier he met and married Lina Billig, another Viennese expatriate. During the middle years of the 1940s two sons, Frank and Charles, were born, both of whom were imbued with the desire Hans had always displayed, namely to seek new knowledge, albeit in different directions. The United States was in the middle of World War II, and gratitude to his newly adopted country made Hans join the US Army as a captain in the Medical Corps, in which he served as a pathologist for two years.

Before his Army service, Hans was appointed Director of Laboratories at Cook County Hospital and was instrumental in founding its Hektoen Institute for Medical Research. When he returned to Chicago after the war he became the director of pathology.

The postwar days at the large medical complex on the west side of Chicago were characterized by bubbling intellectual ferment. This atmosphere was further stimulus to medical research, and the introduction of needle biopsy of the liver provided much previously unseen material. Papers about the pathologic findings in the different diseases of the liver began to flow from the Hektoen Institute. These were often backed up by animal experiments using models resembling human disease.

I entered this exciting mileu as a fellow in pathology at Cook County in the beginning of 1948 and was caught up in the tide of investigation. Thereby began a 40-year association which has not yet ended, since work on Volume IX of *Progress in Liver Diseases,* a series which we started in 1961, continues; the volume will be published in 1989 and will include the last paper Hans wrote. The first major result of our association was the publication in 1957 of *Liver: Structure and Function,* a text devoted to the clinical pathological correlations, the theme to which Hans was so devoted.

At this time The Mount Sinai Hospital approached him to come to New York as director of the Department of Pathology to replace the retiring Paul Klemperer. He accepted this post in 1957 and less than a year later I followed. Hans continued to direct both a busy clinical service department and an increasingly complex research effort with more funding and more space than was available in Chicago.

He had the vision to recognize that the future of Mount Sinai would depend on its ability to start a medical school. After endless hours of discussion with trustees and his fellow department chairmen, Hans began to write about medical education. With the arrival in 1963 of the State of New York charter as a medical school, Hans took the helm as acting dean. He oversaw the development of a new curriculum, heavily emphasizing integration of structure and function in health and disease. He also helped in the planning of the Cummings Basic Sciences Building and later the Annenberg Building. At the same time he began recruiting basic science faculty and a permanent dean, George James.

For five years Hans served as the dean for Academic Affairs as well as the chairman of the Department of Pathology. Hans became the first Irene Heinz Given and John LaPorte Given Professor of Pathology. After the death of George James, he became dean and president in 1972. Despite all this activity, his scientific output continued.

He held these titles until his "retirement" at the end of 1973, when he became a Fogarty Scholar for six months at the National Institutes of Health in Bethesda. Upon his return to New York, Hans became the Gustave Levy Distinguished Service Professor, his title at the time of his death. After retirement he was to pursue scientific interests full time.

Hans took advantage of the new associations he made in Washington and they took advantage of his availability by involving him in numerous research projects, mainly relating to hepatitis B and its appearance in chimpanzees, the pathogenesis of hepatitis B-like infections in the woodchuck and duck, the primary hepatic cancer associated with hepadna virus infections and hepatitis D virus infection around the world. His office on the fourth floor of the Atran Building became an international clearinghouse for histopathology of liver diseases, and Hans was the consultant to the world in matters of the liver. While doing all this work he wrote the yearly Abstract of Abstracts for *Hepatology Rapid Literature Review* and was president and organizer of many of the Falk symposia.

Honors were numerous over the past two decades. He was elected to AOA at Mount Sinai, he received the Friedenwald Medal of the American Gastroenterological Society, the John Phillips Memorial Award of the American College of Physicians, and the Gold Headed Cane of the American Association of Pathologists. He received honorary doctorates from fifteen universities, and he was elected to membership in the American Academy of Sciences and to fellowship in the Academy of Arts and Sciences.

He founded the American Association for the Study of Liver Diseases in 1949, served as its secretary for 10 years and then as its president, and was elected a council member for life. He helped found the International Association for the Study of the Liver and was its second president. He served as associate editor for liver of *Gastroenterology* and also as associate editor for histopathology of *Hepatology*. He was very proud of the accomplishments of his students and coworkers who fill chairs of pathology and other disciplines all over the world. The Department of Pathology at Mount Sinai and the one in Vienna bear his name.

Mount Sinai, pathology, gastroenterology, and hepatology are all indebted to Hans Popper; long after all of us who knew him and worked with him are gone, his influence will still be strongly felt. A warm and touching tribute to Hans Popper was presented in the Stern Auditorium of the Mount Sinai School of Medicine by a few of his many friends, students, and coworkers who were in the audience. This memorial was graciously accepted by Lina with heartfelt thanks to those present and to the many others who sent condolences. Hans himself outlined the plans and program for his scientific memorial, also to be held in the Stern Auditorium in December. He considered this forthcoming meeting to be his thanks for the recognition accorded him by the world medical community. It will, in truth, be a tribute to a great man whose efforts have touched all of us in medicine.

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Pepsin Secretion In Situ: A Review

DONAL F. MAGEE, M.D., PH.D.

It was inevitable that the chief cell should ultimately attract the attention of researchers who like to study physiology in isolated cells rather than in the whole organism. The slowness with which the chief cell was adopted and the relatively small number of investigators compared with the parietal and pancreatic acinar cells is indicative of the position that pepsin has occupied in comparison with other upper-gastrointestinal secretions for the last hundred years.

Pepsin has usually been studied as a secondary issue in experiments designed to investigate the secretion of gastric acid. Gastric juice is known to contain pepsin which is easily estimated—it is a little more demanding than the titration of acid. The secretion of mucus has been almost entirely ignored, I suspect because its determination remains difficult.

This attitude toward pepsin has meant that what data there is, is difficult to interpret. It was not realized until fairly recently—in 1957 (1)—that interpretations based on changes of the constituents of a secretion are unreliable unless the volume of the secretion remains fairly constant. In gastric secretion when acid secretion is zero, the volume of fluid delivered to the collection vessel will also be zero, or close to it, but one cannot assume that the consequent low pepsin figure represents reduced chief-cell secretion. This assumption has of course, been made. On the basis of such spurious interpretation it was concluded that gastrin and a variety of gastrin C-terminal peptides stimulated pepsin secretion from Heidenhain pouches (2). Such experiments were responsible for the long-held view that pepsin secretion and acid secretion were obligatorily linked. Independent secretion is evident today, but it should have been years ago. It is clear now that the water secreted from gastric glands is all hydrochloric acid water (3). Webster (4) refuted an earlier concept that pepsin secretion was associated with the water of the nonparietal secretion.

Basal Secretion

Substantial secretion of pepsin from the empty stomach occurs as long as fluid is secreted or the mucosa is rinsed. Boldyreff (5) noted that volume of juice from the fasted, unstimulated stomach fluctuated regularly, and of course, pepsin could be detected at volume peaks but not between peaks, when there was no secretion. This accounts for reports that pepsin secretion is low or absent in the basal state in dogs. Linde (3), who became aware that the secretion of pepsin was not accompanied by any significant secretion of water, found substantial secretion of pepsin from Heidenhain pouches when he instilled fluid at 10-min intervals. Kleine (6) had found basal secretion of pepsin in transplanted pouches without Auerbach's plexuses. This, of course, is evidence of independent pepsin secretion. Peaking of pepsin secretion at 100-min intervals is evident in the data of Linde (7), although he does not draw attention to it. This was approximately the interval Boldyreff (5) had found between the events that characterized interdigestive activity in dogs. The work of Boldyreff (5) had been completely forgotten until the motility studies of Szurzewski (8) drew attention to the motor characteristics of the empty gut. Verification of secretory periodicity followed quickly.

That fluctuations in pepsin secretion are not an artifact in consequence of fluctuating secretion of fluid was shown inadvertently by Schofield (9). He recorded motility from fluid-filled

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pouches and estimated pepsin therein at 15-min intervals. His data show unmistakable fluctuations, which he noticed, but was unable to interpret. We (10, 11) have noted fluctuations of up to 400% in basal pepsin secretion from both gastric fistulae and Heidenhain pouches. Failure to notice these in the past and the profound effect that these fluctuations have on the responses to cholinomimetic drugs undoubtedly account for past complaints about variability in pepsin experimental data.

The Mystifying Source. The source of the basal secretion has mystified those who have noticed it. It has been called "overflow," implying that it is a measure of the rate at which chief cells, filled with pepsinogen granules, continue to manufacture the enzyme (12). It has been held by some to be absent in dogs and cats (3, 13) and to equal 20%–25% of the maximal vagal stimulated secretion (2-deoxy-D-glucose) in humans (14). Reasons for discrepant results are failure to recognize spontaneous fasting fluctuations and, as in the cat experiments cited above, general anesthesia.

Most who have tried the experiments find that atropine and ganglionic blocking agents reduce basal pepsin secretion (3) but do not abolish it. We have verified this and find that these agents abolish the peaks only, but the level between peaks (the perigee level) is uninfluenced, so that just as with pancreatic secretion, results will be decisively influenced by the phase of the cycle at which one makes the observations (10, 15).

What is responsible for the perigee secretion? It may be the fluid introduced to make collections possible. Linde (3) tested and dismissed this concept, but Zelony, Savitsch, and Savitsch (16, 17) claimed that mechanical stimulation of the fundic mucosa increased pepsinogen secretion. Johnson (18) has been able to increase pepsin secretion in dogs and humans by irrigating the gastric mucosa with HCl solutions in proportion to the concentration used. There were no controls for the effect of volume alone. This effect was blocked by atropine (19). The same applies to the increase in pepsinogen secretion achieved by Harper et al (20) with distention in anesthetized cats. Magee and Hu (21) found progressive increases in pepsinogen secretion with increasing amounts of fluid in Heidenhain pouches in dogs. This relationship was abolished by atropine, but secretion of pepsin continued at a constant low level. In contrast to the findings of Johnson (19), Kondo and Magee (22) claimed that as the pH of fluid placed within a Heidenhain pouch fell, so did the pepsin secretion (2) to reach a steady state starting at pH 4.

The usual basal blood gastrin and/or secretion may be responsible for basal pepsin secretion. However, the evidence against this is that gastrin does not stimulate pepsin secretion from Heidenhain pouches, and from innervated pouches the action of gastrin is antagonized by atropine (15). Burstall and Schofield (23) were unable to detect any significant difference in basal pepsin secretion after antrectomy. Secretin does stimulate pepsin secretion from Heidenhain pouches, but this also is antagonized by atropine. Thus, the stimulus for the constant residual secretion of pepsin seen after atropine is unknown. Since we cannot measure pepsin secretion unless we have fluid in contact with the mucosa, fluid cannot be excluded entirely as a stimulus. Motility was tested as the cause by Schofield (1) and discounted. When mechanical activity ceased, pepsin secretion continued at a low level. Atropine abolishes pouch and fistula motility (10) but, as we have already seen, does not abolish pepsin secretion.

The basal secretion from vagally innervated gastric mucosa is higher than from the denervated, but this difference is atropine sensitive. Splanchnicectomy was found by Schofield (1) to increase basal pepsin secretion from three dogs with Heidenhain pouches, and in transplanted pouches basal secretion fell. We have shown (22) that transection of the trunk containing the left gastric vessels and nerves increases basal pepsin secretion (24). Propranolol does the same (25). It seems, therefore, that the sympathetic innervation exercises a depressant effect on basal pepsin secretion. It is not known whether atropine prevents the increase following sympathectomy, but one suspects that it does.

Stimulation

There is no question today that vagal stimulation, whether electrical in acute preparations or by sham feeding, increases pepsin secretion, along with gastric acid, from the intact stomach. Central vagal stimulation, again either directly or by gastric distention, also stimulates pepsin secretion (21). All of these effects are abolished by vagotomy or by atropine. The effect of vagal stimulation can be mimicked by cholinomimetic agents, and similarly, pepsin concentrations and rate of secretion are much higher than with any other stimulus, but there is a difference from central or vagal stimulation. Vagal stimulation starts promptly and is sustained; cholinomimetic stimulation has to wait for the interdigestive peak before its peak secretion can be obtained only to fall off again rapidly when the peak is past (26). In Heindenhain pouches, vagal stimulation, of course, is without effect on pepsin secretion, but methacholine stimulates acid and pepsin well. The pattern of peak and subsequent fall is exactly the same as in the whole stomach and the effect is atropine sensitive (26).

Gastrin: Some Uninvestigated Enigmas. The actions of all agents known to stimulate pepsin secretion from innervated or denervated stomachs are depressed or abolished by atropine (15), and all of them are much less effective on the vagally denervated than on the innervated stomach (27–29). The extreme example of this is gastrin and its derivatives, which do not stimulate pepsin at all in Heidenhain pouches (30). Secretion, which inhibits acid secretion, is a potent pepsin stimulant in both innervated and vagally denervated pouches (31), and cholinomimetics, of course, stimulate both acid and pepsin. Gastrin stimulates pepsin secretion well from intact stomachs and even from the otherwise intact stomachs of dogs and humans after vagotomy, although much less powerfully (24, 32). It is possible that bilateral vagal blockade does not produce such complete cholinergic denervation as that of the Heidenhain pouch, thus accounting for the difference in the two preparations. This unexplained and curious behavior of the Heidenhain pouch is the probable explanation for the earlier belief that gastrin did not stimulate pepsin at all. Most investigators, like Gregory and Tracy (33, 34), used denervated pouches for their assays and, of course, got no clear-cut response. The addition of small amounts of cholinergic drugs as background with gastrin does not produce any pepsin stimulation above that due to the drug (30). It seems, therefore, that absence or reduction of spontaneous background acetylcholine is not the explanation.

A possibility that has not been investigated is that gastrin stimulates secretion of only one of the two types of pepsin (I and II) and that only the gastrin-insensitive one, which is stimulated by cholinergics and secretin, is to be found in Heidenhain pouches. It is true that the gastric glands, especially the chief cells, undergo atrophy in vagally denervated pouches. This curiosity remains to be resolved and continues almost uninvestigated. The difference between the vagally denervated stomach and the Heidenhain pouch with respect to pepsin is a special enigma. It might well depend on the absence of gastric content plus vagal denervation in the pouch.

Gregory and Tracy (33) claimed that single injections of large doses of gastrin depressed either gastrin or histamine-stimulated acid secretion, but as the inhibition was waning, that is, as the volume of secretion was increasing, a great increase in pouch pepsin was noted. This has been verified by Konturek and Grossman (35) and has been seen when histamine stimulation was depressed with acetazolamide or cholecystokinin (36). It may, therefore, be a consequence of the inhibition of acid secretion rather than a direct action of gastrin on chief cells. Washout is a possibility. There seems to be no report of investigations of this effect in recent years, nor of experiments in which the volume of fluid in the pouch was substantial and constant in amount.

Does Histamine Stimulate Pepsin Secretion In Vivo? A similar phenomenon may be the basis for the controversy surrounding histamine. Some say it stimulates pepsin secretion, an equal number say it does not (37). Early experiments in which single doses of histamine were used produced a transient increase in pepsin that those in opposition attributed to a simple flushing effect. Bucher et al (38) used repeated doses of histamine in vagotomized dogs with gastric fistulae. They claimed, and their graphs show, a sustained increase in pepsin output. Uvnas, with cats (39), and Linde, with both dogs and cats (3), hold that histamine did not stimulate chief cells. Linde (3) used Heidenhain pouch dogs.

In our hands (40) histamine did not increase the secretion of pepsin, but it greatly augmented the pepsigogic effect of secretin on Heidenhain pouches. This has been seen also in anesthetized cats (41), but Gillespie and Grossman (42) were unable to demonstrate potentiation between bethanecol and histamine. Hirschowitz (27) has claimed stimulation of pepsin in animals with gastric fistulae and fundic vagotomy, but in the latest study of Hirschowitz (43) 50 mg/kg/hr of histamine in gastric fistula dogs did not stimulate pepsin secretion in control studies.

No one today, quite understandably, seems to be much concerned whether histamine stimulates pepsin secretion in vivo or not. The effect, if there is one, is likely to be small, and thus likely to be masked unless periodic fasting secretion is controlled for. Secretory peaks of 100 min are evident in some of the curves of Bucher et al (38), representing experiments in a single animal.

Following meals, rapid pepsin secretion

starts as a result of the cephalic phase of gastric secretion. This secretion continues, it is believed, until food leaves the stomach. Once the cephalic phase is over, one might expect a decline in the rate of pepsin secretion, since the gastrin-stimulated maximum is less than one-fourth of the vagally stimulated secretion (44). This is not the usual finding.

It is supposed that the presence of food in the lumen of the stomach sets off vagovagally mediated, distention-stimulated secretion, giving a mixture of low pepsin hormonal secretion and high pepsin vagal secretion. It is true that in humans following vagotomy, pepsin secretion is diminished. This cannot be explained wholly by the loss of vagovagal distention reflex, because the secreting mucosa after vagotomy is less sensitive to gastrin.

In the past the efficacy of gastrin as a pepsin stimulus was doubted and disputed. The probable reason for this, as explained above, is the failure of gastrin to act on vagally denervated pouches. This means that gastrin does not fit all the classical criteria of a hormonal pepsigogue, but nevertheless it is the orthodox wisdom that endogenous or exogenous gastrin even from a denervated pyloric pouch will stimulate pepsin secretion from the intact fundic mucosa. What is the evidence for this view? Following meals or intravenous gastrin, pepsin secretion increases from intact stomachs with or without intact vagi, from Pavlov pouches, but not from Heidenhain pouches (9). (The classical Pavlov pouch is usually in continuity with the main stomach.) Whether it still increases from Pavlov pouches after vagal denervation is unknown.

Experiments in which the entrance of gastric acid into the duodenum is prevented have not been done in dogs, but they have been performed in anesthetized cats (45); gastrin and its analogues did not increase pepsin secretion. In experiments in humans with gastric and duodenal suction, pepsin rose only when the duodenum became acid (46). Olbe et al, using antrectomized dogs, found that sham feeding raised pepsin, but intravenous gastrin not only did not raise, but actually diminished pepsin (47). It is now well known that pepsin secretion is stimulated by simple distention of the stomach and also by an acid pH. Dritsas and Kowalewski (48), who used isolated stomachs perfused by gastrectomized donor dogs, found that intravenous histamine raised pepsin only when the luminal pH was between 2.4 and 1.7. Perhaps these findings account for the failure of gastrin to stimulate pepsin secretion from Heidenhain pouches.

Is Secretin a Pepsigogic Hormone? So the evidence that gastrin is a pepsigogic hormone is doubtful. What of secretin? It certainly is, but is it physiologic?

How gastrin acts, when it does, is not clear, since pepsin secretion—whether stimulated cholinergically or hormonally—is blocked easily by atropine or by ganglionic blocking agents (4). Gastrin stimulation of Heidenhain pouch acid is not affected by ganglionic blockade, and innervated stomach acid is only slightly reduced; thus with blockade the effect of gastrin is to produce a high acid and very low pepsin juice (15). Secretin, on the other hand, produces high pepsin secretion and no acid (31). This also is blocked by atropine. Pepsin secretion seems, therefore, clearly to involve some nicotine cholinergic intermediary, hence the feeling that background acetylcholine release in the fully innervated mucosa is responsible for the much higher responsiveness than in denervated mucosa.

If histamine is involved in the secretion of pepsin, H_2 blocking agents should depress it. These agents, if anything, seem to increase cholinergically stimulated pepsin and to reduce hormonal stimulation, but to a much lesser extent than acid secretion (49). So here again we get little help with the histamine problem. Studies in humans usually show a fall; even omeprazole, which specifically blocks the specific H^+ transport mechanism, does so (50), but this is hard to evaluate since the volume of secretion is drastically reduced as well.

Following feeding, pepsin secretion from Heidenhain pouches is very different from that of innervated Pavlov pouches. In the latter, both acid and pepsin rise as expected, but in the former, acid secretion increases yet pepsin—after an initial, variable rise—falls consistently to much below control levels; pouch motility declines also. This phenomenon was first systematically documented by Schofield (9). He was able to show that it persisted in transplanted pouches and was, therefore, independent of extrinsic innervation. He correlated the suppression of pepsin by feeding with the decrease in motility, but mechanical stimulation that increased motility did not increase pepsin.

We have already seen that gastrin does not stimulate pepsin secretion from Heidenhain pouches, but it does stimulate acid secretion (30). On the other hand, acid duodenal contents cause liberation of secretion, which inhibits motility but is a potent stimulant (31). Closure of a gastric fistula in secreting stomachs reliably raises pepsin secretion from a coexisting Heidenhain pouch, but we have shown that this pepsigogic effect of secretion can be antagonized by pentagastrin (51). Whether such an antagonistic action occurs physiologically between gastrin and secretin is unknown, but even if it does, control levels of pepsin and motility would be seen, rather than a depression of both. Atropine and ganglionic-blocking agents cannot be used to sort this out since they depress both basal, secretin-stimulated and gastrin-stimulated motility and pepsin (15). It seems, therefore, that even though secretin can stimulate pepsin, evidence that this is a physiologic role is not strong. There are other putative pepsigogic hormones: bombesin, motilin, and VIP, for example, but the evidence for or against a physiologic role is even more skimpy than for gastrin or secretin.

Duodenal Inhibition? Cholecystokinin liberated when the duodenum becomes very acid and by protein and fat digesta in the duodenum can depress acid and pepsin secretion and motility (52). Whether this is physiologic is disputed. A piece of evidence in favor of some inhibitory influence from the duodenum is that ganglionic-blocking agents *increase* pentagastrin-stimulated acid secretion from Heidenhain pouches (53). This increase is much greater if the gastric fistula is closed (54). As far as pepsin is concerned, this is very indirect because these blocking agents block all forms of pepsin stimulation. On looking over many past experiments of our own it is evident, but unpublished, that pentagastrin depresses Heidenhain pouch pepsin secretion. In the usual experiment this effect is slight (51), but consistent enough to be convincing. Similar examination of old data has revealed that pentagastrin does not increase pouch pepsin even when the stomach and duodenum are kept alkaline. To date, this is the extent of these studies.

Another Pepsigogic Hormone? From time to time a specific pepsin-stimulating hormone apart from gastrin has been suggested. If there is one, it is hard to understand why it does not stimulate chief cells in Heidenhain pouches following meals unless it is true, as suggested earlier, that the sensitive cells in the pouch are degenerative, or that mechanical stimulation is needed as well. Pratt (55), Babkin and Komarov (56), Braganza et al (57), and others have claimed a pepsigogic substance in extracts of small bowel mucosa distinct from secretion and cholecystokinin. Blair et al (58) found that extracts of pig duodenal mucosa and gastric antral and fundic mucosa when given intravenously raised pepsin secretion. They called the hypothetic pepsin stimulant gastrozymin. Blair et al (59) claimed that their gastrin contained a pepsin stimulant. A large part of this controversy is undoubtedly due to the failure of gastrin to stimulate pepsin secretion from Heidenhain pouches. Some early workers (16, 17) have claimed that distention of the main stomach with a balloon raised pepsin and acid secretion from denervated pouches; however, these experiments cannot be used to establish a hormonal stimulation of pepsin since the water of the secretion is all HCl water. Uvnas (60) concluded from his own and past experiments that there was sufficient evidence for a pepsigogic hormone in the pyloric mucosa.

In 1964 Blair et al (61) injected pure secretin into anesthetized atropinized cats and found an increase in pepsin secretion. This is curious since, in later experiments in dogs, we found that the pepsigogic effect of secretin was suppressed by atropine. In 1968, in dogs, we (31) noted that Heidenhain pouch washings became turbid when secretin was given intravenously. Pepsin was found to be markedly increased according to the dose. This has since been verified consistently in dogs, humans, and pigs. It is hard to find any reference to gastrozymin today. Secretin seems to fill the bill, and the subject seems to have been left at that. Glucagon, which resembles secretin closely in structure and action, oddly enough does not increase pepsin secretion (62).

The action of gastrin on pepsin secretion seems to be one of tacit acceptance that it does stimulate pepsin secretion from vagally innervated stomachs, less so following bilateral vagatomy and not at all in Heidenhain pouches. In this unsatisfactory state the subject has virtually been abandoned. Current fashion has removed investigators from the physiologic problems of pepsin secretion onto the isolated-cell roundabout.

Summary

Studies devoted to pepsin secretion are few and hard to interpret. Early studies are vitiated by uncontrolled fluctuations in the volume of gastric juice, and the tendency to consider results obtained from Heidenhain pouches as applicable to the intact stomach.

There is a basal pepsin secretion that shows marked regular interdigestive fluctuations in phase with the mechanical aspects of the phenomenon. The mechanism underlying the resting secretion is unknown.

It is commonly assumed that gastrin stimulates pepsin secretion, but the evidence for this is inconclusive. Gastrin, either exogenous or endogenous, fails to stimulate pepsin secretion from Heidenhain pouches. Gastrin and meals stimulate pepsin secretion from the intact stomach or innervated pouch, but whether this is direct, due to secretin release from the duodenum, or due to mechancial or chemical stimulation of the secretory mucosa has not been investigated.

Effective stimulation, whether by gastrin in intact stomach or by parasympathetic drugs in innervated or denervated gastric mucosa, is greatly diminished by atropine and ganglionic blockade, suggesting nicotinic ganglionic parasympathethic mediation, but only atropine depresses the pepsigogic action of secretin.

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Neuroendocrine Abnormalities and The Pathogenesis of Estrogen-Receptor-Positive Breast Cancer

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Abstract

Breast cancer in women appears to have different manifestations, depending on the presence or absence of the estrogen receptor (ER). Although both ER-negative and ER-positive breast cancers are likely to be associated with the presence of an oncogene, ER-positive breast cancer is also associated with two clinical neuroendocrine abnormalities involving the pineal gland and olfaction, both of which may result from a defect in tryptophan metabolism along the kynurenine pathway.

Recent studies of the epidemiology, genetics, and endocrinology of breast cancer suggest that this neoplasm occurs in at least two distinct forms, depending on estrogen receptor (ER) status.

Epidemiology

There is marked variation in the incidence of breast cancer in different areas of the world (1, 2). The disease is five times more common in the United States than in Japan or other areas of the Far East (3). This disparity is not genetic, since first- and second-generation Japanese women in San Francisco have rates higher than do women in Japan (4).

The geographic variation of breast cancer incidence correlates with dietary differences, particularly fat intake (5). In Japan, average dietary fat intake is low, whereas in the United States dietary fat intake is high (6). In addition, Seventh-day Adventists, who have lower-than-average fat intake because many are vegetarians, have lower breast cancer death rates than the general population (7); however, socioeconomic status may be a confounding variable (8).

Even within low- and high-risk countries, breast cancer incidence varies. In Japan, a "low-risk" country, the rate of breast cancer decreases after menopause, while in Sweden, a "high-risk" country, there is a continued increase of incidence with age beyond menopause. These patterns suggest multiple etiologies and manifestations of breast cancer (9).

Genetics

Family history is a key risk factor in breast cancer (1) and is particularly important if the cancer is bilateral or if there is male or female breast cancer in other family members (10). Further evidence of the genetic nature of breast

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cancer may be inferred from the weak association with HLA antigens (11) and cerumen type (12).

This genetic evidence has spurred the search for a specific transforming gene, an oncogene, that is responsible for human breast cancer. One study, for example, demonstrated that the same or closely related transforming genes were activated in six different mouse mammary carcinomas induced by the mouse mammary tumor virus or the carcinogen dimethylbenzanthracene (13). Another study reported the detection and cloning of a Harvey H-ras oncogene from the HS578T human mammary carcinoma cell line derived from a rare, highly malignant tumor with histopathologic features of both carcinoma and sarcoma (14).

A third study described the amplified function of a novel v-erb-B–related gene in a human mammary carcinoma (15). This gene appears to encode a truncated version of the receptor for epidermal growth factor, which may be responsible for the proliferation of malignant cells.

Despite these data, transforming genes appear to occur at a relatively low frequency in human mammary tumors. Krause et al (14) observed no oncogenes in four human breast carcinoma cell lines and 16 primary human breast carcinomas. Furthermore, truly hereditary breast cancer is not common. Only about 5% of all patients fulfill criteria allowing their disease to be classified as autosomal dominant (10).

Some oncogenes seem to render the tumor hormone independent and estrogen receptor (ER) negative. One experiment confirming this effect was performed by Kasid et al (16) on the MCF-7 human breast cancer cell line. MCF-7 cells require substantial estradiol levels for tumor formation in vivo. However, when the v-ras^h oncogene is inserted into these cells, they no longer demonstrate augmented growth in culture in response to estrogen, and proliferation is minimally inhibited by antiestrogens (16). Moreover, in a study of 104 primary human breast tumors, Sainsbury et al (17) found that the epidermal growth factor receptor, which is associated with the erb-B oncogene, is also associated with ER-negative lesions.

Endocrinology

A strong association has been found between breast cancer and hormones, especially estrogen, progesterone, and possibly prolactin (18). The risk of breast cancer is 100 times greater in women than in men, and the disease does not occur before puberty. The risk of breast cancer increases as the age at menarche decreases and as the age of menopause increases; that is, the longer a woman has normal ovarian function, the greater her risk. Furthermore, daughters of women with breast cancer have elevated mean 24-hr prolactin levels and a partial resistance of prolactin to dopamine suppression (19). This aberration suggests a neuroendocrine abnormality, since the secretion of estrogen, progesterone, and prolactin are under neuroendocrine control. Hourly pulses of gonadotropin-releasing hormone (GnRH), produced by the arcuate nucleus of the hypothalamus, stimulate the anterior pituitary to elaborate the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH stimulate the ovary to produce estrogen and progesterone. Prolactin production by the anterior pituitary is regulated by prolactin-inhibiting factor (PIF). The control mechanism for PIF appears closely related to that for GnRH and resides within the same area of the hypothalamus (20).

We postulate that a neuroendocrine defect within this control mechanism might promote or predispose to ER-positive breast cancer. Recently identified abnormalities involving the pineal, olfaction, and tryptophan metabolism suggest such a defect is associated with ER-positive breast cancer. The data to support this hypothesis are as follows.

The pineal gland, its principal hormone melatonin, and breast cancer are strongly interrelated (21). There is a decreased nocturnal plasma melatonin peak in women with ER-positive breast cancer (22, 23), and melatonin inhibits, whereas pinealectomy enhances, dimethylbenzanthracene-induced mammary tumors in the rat (24).

Pineal function is related to sense of smell (25), and women with ER-positive breast cancer have abnormally diminished olfaction (26). Since efferent olfactory impulses pass via the median forebrain bundle to the entire lateral extent of the hypothalamus (27), and since normal mammalian pineal function is dependent on the suprachiasmatic nucleus of the hypothalamus (28), we hypothesize that both the pineal and olfactory abnormalities share a common hypothalamic origin, possibly the result of a neurotransmitter defect involving serotonin.

The amino acid L-tryptophan is a precursor of both melatonin and serotonin. Moreover, tryptophan abnormalities are associated with breast cancer (29, 30). After an oral 2-gm load of tryptophan, urinary levels of tryptophan metabolites of the kynurenine pathway are high in most women with breast cancer. Using the assay method of Arend et al (31), we recently measured total kynurenine in 24-hr urine samples from women with early-stage breast cancer given a 2-gm oral tryptophan load. The following values were obtained for women with ER-positive and -negative tumors:

	ER+	ER−
No. of subjects	11	10
Kynurenine (μmol/day)	33.0 ± 28.7	12.2 ± 5.6
Significance	$p < 0.05$	

The higher kynurenine excretion in ER-positive subjects suggests a defect in tryptophan metabolism. Whether this abnormality is responsible for the melatonin abnormality of these subjects and the olfaction abnormality, however, cannot be determined from these observations. Nonetheless, it is interesting to speculate that these derangements are the result of a genetic defect in tryptophan metabolism, which diverts tryptophan from the serotonin pathway to the kynurenine pathway. The observation of high kynurenine excretion associated with a reduced relapse rate in premenopausal women with stage I or stage II breast cancer (32) is consistent with this hypothesis, since ER-positive breast cancer has a longer natural history than ER negative (33).

Further evidence for a neuroendocrine abnormality is suggested by the relationship of body fat to both the onset of menarche and the risk of mammary neoplasms. Girls who are fat have menarche early, whereas girls who are very slender have a considerable delay in the onset of menses (34). This delay appears to result from a modification of the activity of the arcuate nucleus of the hypothalamus (35). Furthermore, thin women have a decreased risk of breast cancer, whereas fat women have an increased risk (1). Thus, body habitus appears to influence the same neuroendocrine regulatory mechanism that is responsible for both fertility and the predisposition to breast cancer. This influence might result from the fact that free fatty acids disturb the ratio of bound to free tryptophan in plasma. The free fatty acids cause increased free tryptophan, which is able to cross the blood-brain barrier (36).

Other recent findings suggest that the described neuroendocrine defects function in concert with an oncogene to induce ER-positive breast cancer. First, the human estrogen receptor c-DNA shows sequence, expression, and homology to the erb-A oncogene (37). Second, the normal mouse myc gene, with large portions replaced by hormonally inducible mouse mammary tumor virus (MTV) DNA, has been inserted into mouse embryos. The resulting transgenic mice spontaneously develop mammary carcinomas, but only during the second or third pregnancy (38). The MTV/myc fusion gene alone is not sufficient to induce breast cancer. Therefore, hormonal and possibly neuroendocrine changes, perhaps somewhat comparable to those associated with a predisposition to develop human breast cancer, are needed to induce the breast cancer in the transgenic mice.

An interesting psychoendocrine feature of breast cancer is its relationship to depression. In early breast cancer, recurrence-free survival is reduced in depressed patients who respond to their disease with stoic acceptance or feelings of helplessness and hopelessness; survival is much better in women who initially react to their cancer with denial or who have a "fighting spirit" (39). In addition, the nocturnal melatonin peak is reduced in depressed patients (40), just as it is in women with ER-positive breast cancer. Also, cortisol is elevated in both depressed patients (41) and women with breast cancer (42–44). If the pathogenesis of ER-positive breast cancer and certain forms of depression share anything in common, antidepressant drugs might be of value in breast cancer chemoprevention in high-risk women.

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A New Technique for Control of Epicardial Bleeding

Aurelio Chaux, M.D., and Carlos Blanche, M.D.

Abstract

Epicardial denudement and subsequent profuse bleeding can occur during cardiac reoperations and poses the potentially difficult problem of bleeding control. To solve this problem a new, simple technique has been devised; it consists of using a piece of pericardium as a patch, sewn to the myocardium and packed with absorbable bovine microfibrillar collagen to completely cover the denuded and bleeding site. This technique was used clinically in two patients during myocardial revascularization, with complete resolution of the problem.

Epicardial denudement can occur during dissection of pericardial adhesions produced by prior surgery, myocardial infarctions, or inflammatory processes of the pericardium. It can also be the consequence of a trauma produced when the heart is held upward to revascularize the posterior or inferior branches of the circumflex and right coronary arteries, especially in old patients with soft and friable tissues.

Simple and small epicardial bleeding can be controlled with electrocautery or direct suturing techniques; however, a deep and extensive area of denuded epicardium can turn into a difficult problem because of uncontrollable bleeding, particularly if the patient has abnormal coagulation parameters.

Methods

This technique uses a piece of pericardium slightly larger than the damaged epicardium, and shaped accordingly. The patch is sewn with superficial bites of 4-0 or 5-0 Prolene, avoiding injury to branches of the coronaries and going around the raw myocardial surface. Before the suture line is completed, absorbable microfibrillar collagen hemostat (Avitine, Alcon Laboratories, Fort Worth, Texas 76134) is packed into the pocket created by the pericardial patch to produce hemostasis (Fig. 1). Then the suture line is completed and the nonexpandable pericardial patch prevents displacement of the microfibrillar collagen, helping to tamponade the bleeding and replacing the nonexisting epicardium (Fig. 2).

Case Reports

Case 1. A 72-year-old woman underwent myocardial revascularization for crescendo angina pectoris in June 1986. She had had previous coronary bypass surgery for triple-vessel disease seven years previously, and three of the four grafts were occluded. During the dissection of the pericardial adhesions, an area of the posterior myocardium, 2 × 2.5 cm in diameter, was deprived from its epicardial cover. This area continued to bleed profusely, even after heparin was totally neutralized. Conventional methods failed to control the bleeding, and a decision was made to use the pericardial patch technique as it was previously described, to cover the exposed myocardium. The bleeding was completely and promptly controlled by this method, and the patient made an uneventful recovery.

Case 2. A 73-year-old woman underwent coronary bypass surgery for severe triple vessel disease in February 1987. She had had bilateral mastectomy for carcinoma seven years pre-

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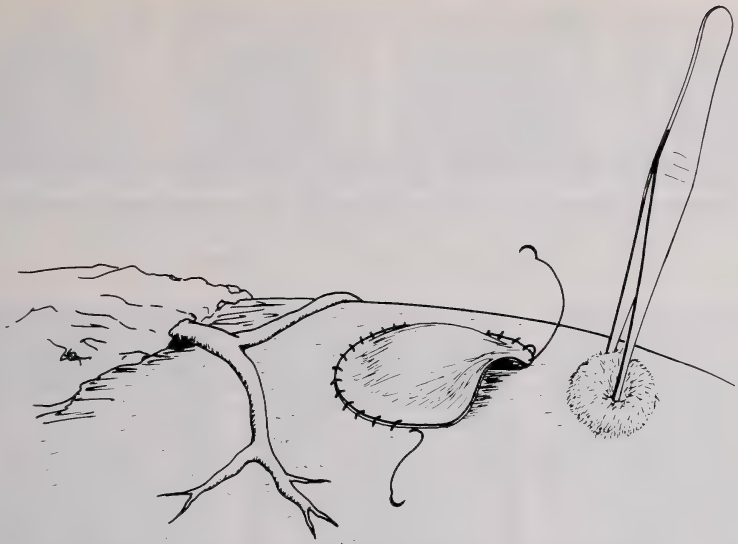

Fig. 1. Pericardial patch being sewn circumferentially. Absorbable microfibrillar collagen is packed into it before suture line is completed.

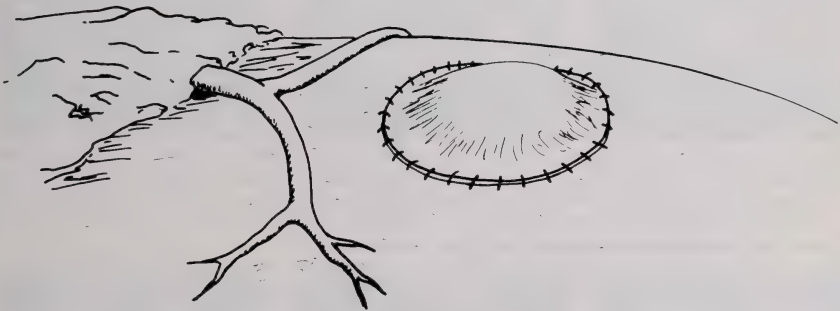

Fig. 2. Completed patch covers entire denuded area, controlling epicardial bleeding.

viously, although no radiation or chemotherapy were used postoperatively. During the operation it was seen that the tissues were extremely friable and an area of 3.5 × 3.5 cm in the postolateral wall was denuded of epicardium. The pericardial patch technique was used successfully after all other standard methods failed to control the profuse bleeding. The patient recovered satisfactorily.

Discussion

If the epicardium is accidentally removed from the surface of the heart, significant bleeding can occur, and at times this bleeding may be difficult to control by conventional methods. Autologous pericardium can be used to replace the lost epicardial surface to completely seal the bleeding area and to hold in place the absorbable microfibrillar collagen that serves as the mattress for the formation of clots. Autologous pericardium is almost always available for this purpose, it is easy to handle, and it accommodates very well to the shape and size of the bleeding area.

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Uncommon CT Patterns of Subdural Hematomas Managed Nonsurgically

JOHN O. LUSINS, M.D., EDWARD DANIELSKI, M.D., AND SHARON KREPS, M.D.

Abstract

Since the introduction of nonsurgical management of subdural hematoma in the early 1960s, this approach has been accepted by the medical community as an alternative mode of treatment of a stable patient with subdural hematoma. The availability of CT scanning has permitted the rapid diagnosis and easy follow-up of such patients. In most instances, the clinical course is predictable, and the outcome is favorable, as reported in a number of series. However, in our own series of over 250 patients, we have noted that certain patients have courses that deviate from the expected and yield a CT scan significantly different from the conventional.

CT scanning of the head provides an ideal means of following patients who are being managed nonsurgically (1–3). The study can be carried out rapidly, and any change in size of the subdural hematoma can be readily recorded and, if need be, dealt with. In most instances, the progression of the case is clear-cut; the patient's subdural hematoma gradually becomes smaller and eventually resolves over a number of weeks to a few months.

Occasionally, a patient develops a CT scan pattern which is significantly different from that expected and therefore worth isolating and presenting in greater detail. Each situation is discussed independently.

Clinical Material

Collapsing Membranes. One unusual pattern was noted in a patient who was 68 years of age and had a large subdural hematoma with shift of the midline. The subdural gradually resolved. However, when resolution was complete, it was noted that the sulci over the hemispheres where the subdural hematoma had been were not as clearly delineated as those on the opposite side. The findings did not change even when the patient was rescanned two years later (Fig. 1).

The explanation that we proposed is that the patient, during the course of his subdural hematoma, developed significant membranes surrounding the subdural hematoma. As the fluid reabsorbed, the membranes collapsed and acted as a mantle and blurred the clear delineation of the sulci.

Another well-documented presentation of this pattern was noted in a 72-year-old patient who initially had bilateral subdural hematomas as well as a moderate degree of preexisting cortical atrophy. The collapsing subdural membranes were therefore unusually well outlined (Fig. 2). We could eventually observe their complete collapse and persistence after the subdural fluid had reabsorbed.

Calcified Membrane. Another type of unusual CT pattern occured in a 65-year-old man who initially had bilateral subdural hematomas secondary to a relatively minor auto accident in 1978 (Fig. 3). After the diagnosis was made, he was admitted to the hospital and was noted to be in stable condition. He was treated with bedrest and steroids. A repeat CT scan, performed one

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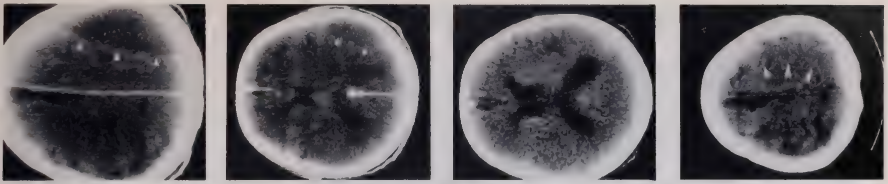

Fig. 1. **From left, 1 and 2** A 68-year-old man who sustained head trauma developed left-sided subdural hematoma (arrows) with shift of midline from left to right. **3 and 4** Repeat CT scan two years later shows complete resolution of subdural hematoma on left. However, there is now opacification of sulci on side of previous subdural hematoma (arrows).

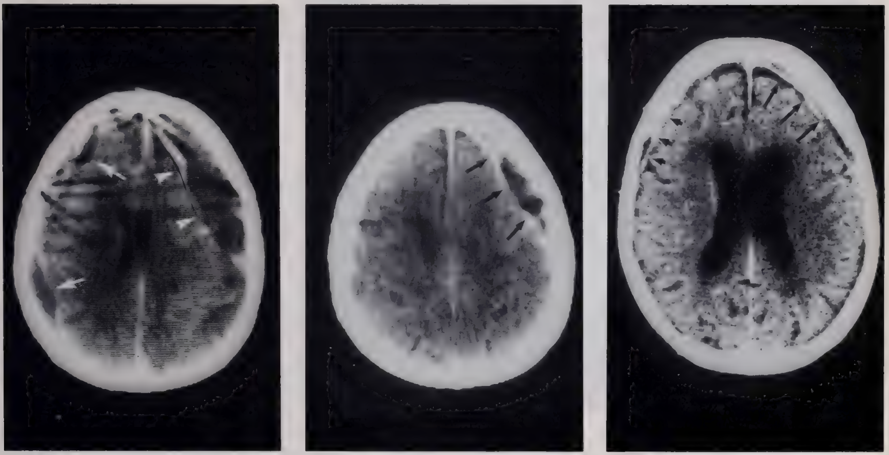

Fig. 2. **Left** A 72-year-old man with bilateral subdural hematomas after a head injury (arrows.) **Middle** Six weeks later right-sided subdural hematoma is almost completely resolved. Subdural hematoma is still present on left and is surrounded by well-delineated membrane (arrows). **Right** Six months later bilateral hematomas have resolved but a thick membrane persists on left (long arrows). Membrane on right is less prominent (short arrows).

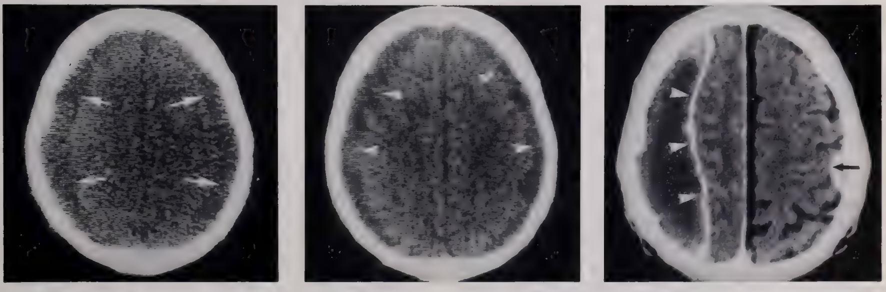

Fig. 3. **Left** A 63-year-old male with bilateral subdural hematomas after a minor automobile accident (arrows). **Middle** A month later, bilateral subdural hematomas are smaller than on initial scan. **Right** Five years later, a large subdural hematoma is present on right, surrounded by thick, calcified membrane (white arrows). Small parietal subdural hematoma is present on left (black arrow).

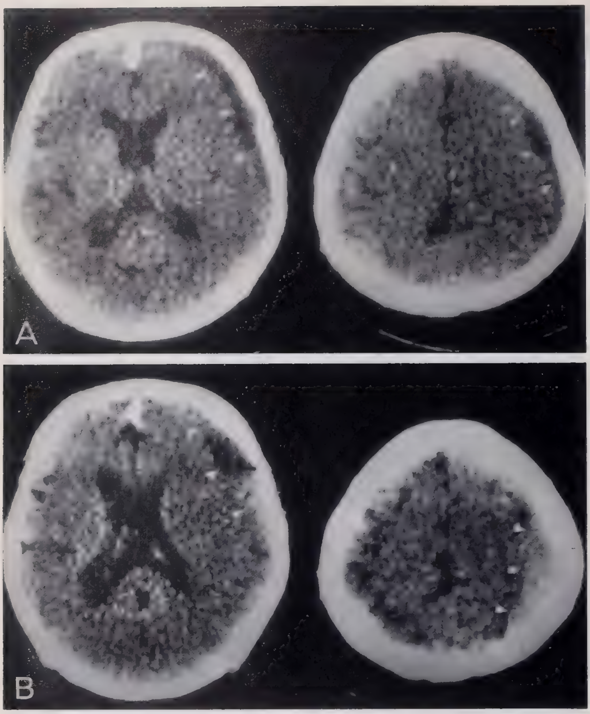

Fig. 4. A CT scan four weeks after initial diagnosis of subdural hematoma demonstrates persistence of small subdural hematoma on left (arrows). **B** Two weeks later, subdural hematoma has enlarged and also demonstrates double density, indicating bleeding into hematoma (arrows).

month later, still showed bilateral subdural hematomas, which were thought to be smaller. The physician in charge felt that the patient would continue to improve and could be followed up as an out-patient. However, he was lost to further neurological follow-up until 1983, when he was seen by another neurologist for minor, transient ischemic attack. A CT scan at this time showed that the subdural hematomas, rather than resolving, had become static and encapsulated with a membrane that was calcified. The right-sided one was significantly larger than the left. The patient at this time had no evidence of localizing neurological symptoms.

Rebleeding into Resolving Hematoma. Another CT pattern which stands out was noted in a 60-year-old patient with mild hemiparesis and headaches after a minor head injury. A subdural hematoma was diagnosed and he was treated nonsurgically. He gradually improved. At the time of the second scan, four weeks later, the subdural hematoma was significantly smaller (Fig. 4). He was being followed up at home; about two weeks after the second scan, he noted some worsening of his symptoms. He had recurrence of headache and weakness. A CT scan was immediately performed and we were able to demonstrate not only the presence of the old subdural hematoma which was hypodense, but evidence of rebleeding into it with enlargement of it and delineation of fluid level between the hypodense old fluid and the isodense recent bleeding. Because of his worsening condition, the patient underwent surgery.

This case made us suspect that rebleeding into a resolving subdural hematoma was probably the cause of deterioration of an initially improving patient.

This conclusion was reinforced by a second case of a 64-year-old man who four months prior to the evaluation by us, fell from the roof of a porch he was repairing. He stated that he struck his head but did not lose consciousness. He had a mild headache for a week but did not seek medical help. However, seven weeks after the accident, he presented in the emergency room with a left hemiparesis which had developed over the previous 12 hours. A recent head injury was not documented. The physician in the emergency room felt that the patient had a cerebral vascular accident and CT was performed. Rather than finding ischemic changes on the scan, we demonstrated that the patient had bilateral, old, hypodense subdural hematomas. We attribute these to his previous fall. However, we also noted that he had rebleeding into the left subdural hematoma (Fig. 5).

We postulated that the rebleeding on the left produced his recent symptoms due to acute enlargement of the hematomas. The patient was treated nonsurgically and eventually both subdural hematomas resolved.

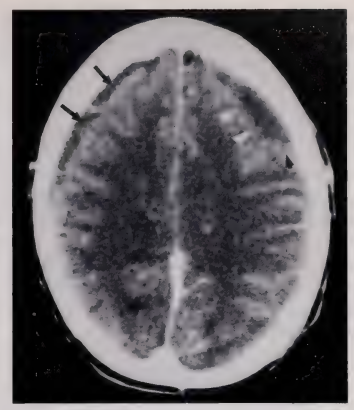

Fig. 5. CT scan of 65-year-old man seven weeks after he sustained head injury. He was asymptomatic until he had rapid onset of right-sided hemiparesis and a CT scan was performed. Scan shows bleeding into hypodense hematoma on left (white arrows) with resultant double density (short black arrow). Small hematoma on right is hypodense.

Discussion

The nonsurgical management of subdural hematomas was introduced in the early 1960s (4–5). There was an initial reluctance to accept this modality based on the fact that once the diagnosis of subdural hematoma was made angiographically, the physician had to rely on the clinical course of the patient to ascertain improvement. If it appeared that the patient was not improving, repeat angiography had to be carried out. Many physicians felt that the potential need for repeat cerebral angiograms, with their associated morbidity and general discomfort to the patient, was not an acceptable alternative to immediate surgical intervention. The introduction of nuclear brain scanning permitted somewhat easier follow-up of patients not operated on for subdural hematoma. However, frequently the nuclear scan did not directly correlate with patient improvement. There were frequent false-negative scans. Also, positive scans tended to remain positive, lagging behind the patient's clinical improvement (6).

The availability of cranial CT has provided rapid, reliable, and noninvasive means of following subdural hematoma size. At present, therefore, if a patient with subacute or chronic subdural hematoma is in a stable condition at initial presentation, nonsurgical management becomes a viable alternative.

Over the last 18 years, we have collected over 250 cases of nonoperated-on subdural hematomas in which the patients were followed up sequentially until the referring physician felt either that the patient's subdural hematoma had resolved, or that the patient was clinically at the point at which it could be safely assumed that the subdural hematoma had become small enough to discontinue further follow-up. Bender and Christoff (7), in an initial series of 100 of these cases, described the selection, clinical management, and outcome of these patients.

From the cases observed, some conclusions can be drawn about the behavior of nonoperated-on subdural hematomas. In most instances the course is uneventful; the subdural hematomas completely resolve with time. However, there is no certain means of predicting size, configuration, degree of membrane development, or length of time for resolution. In most instances, at the end of resolution, the two cerebral hemispheres appear the same on CT. On occasion, if the hematoma has developed a significant membrane, this membrane may collapse and partially obscure the sulci on the side of the hematoma.

In rare instances, the hematoma may not resolve but may remain unchanged for many years, its membranes becoming calcified. Therefore, it is imperative that even though the patient is improving, follow-up be carried out until the hematoma has completely resolved.

It is well known that a patient whose clincial course has been stable may show signs of deterioration as a result of sudden enlargement of the hematoma. The time-honored explanation has been that the expansion was caused by increased osmolarity of the subdural fluid due to the build-up of albumin from the abnormally permeable blood vessels of the highly vascular membranes surrounding the subdural collection (8). However, subsequent demonstration, by the introduction of radionuclide-tagged albumin, that the permeability of the membrane is bidirectional has made this explanation less plausible (9). We feel that the more acceptable explanation for the deterioration of a patient who was previously doing well while on nonsurgical management is that there has been recent rebleeding into the hematoma collection.

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Risks of Lumbar Puncture in the Presence of Intracranial Mass Lesions

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Abstract

Prior series evaluating the risk of performing lumbar puncture (LP) have not had available computed-tomography (CT) scan to confirm or rule out intracranial lesions, which have been thought to increase the hazards of LP. To further study the risk of LP, we prospectively evaluated 38 patients with intracranial mass lesions documented by computed tomography (CT) who underwent diagnostic lumbar puncture (LP). All patients but one were neurologically stable or improved 48 hr later. One patient who had fixed, dilated pupils and absent caloric reflexes before LP died. Lumbar puncture carries little, if any, measurable risk to most patients with CT-documented intracranial mass lesions.

According to some authorities (1), lumbar puncture (LP) can be hazardous in patients with intracranial mass lesions. Owing to pressure-gradient formation and herniation across the tentorial incisura or foramen magnum, patients could, theoretically, deteriorate after LP. LP-related worsening is rare, however, in reported series of unselected patients with masses or intracranial hypertension (2–6). Because of the urgency in performing LP in patients with suspected bacterial meningitis in whom intracranial mass has not been ruled out, it is necessary to know the risk of this procedure with some certainty. Previous series to evaluate this risk suffered from not having computed-tomography (CT) scan confirmation of the intracranial lesions causing increased pressure and were forced to rely solely on the neurologic examination.

Methods

We prospectively evaluated patients with CT-documented intracranial mass lesions (excluding acute cerebral infarction) who had LP at Lincoln Hospital (Bronx, NY) from July 1982 to June 1985. All patients meeting these criteria were eligible for the study. We believe that most eligible patients were included, owing to our prospective case-finding and the high rate of neurologic referral at our institution. Six patients were excluded because of inadequate documentation; none of these had any noted deterioration following LP. Patients with undocumented intracranial mass (that is, CT not performed) and LP are not included.

LP was performed in each case to rule out meningitis. In most cases, CT scan (documenting intracranial mass as a cause of neurologic impairment) had not been performed at the time of LP, but was obtained within one week. All but four CT scans showed mass effect, that is, distortion of ventricles, cisterns, or sulci; in the four exceptions, inferior CT quality prevented determination of sulcal pattern, and mass effect was inferred from size of the lesion. We noted changes in mental status, pupil reactivity, eye movements, respirations, and other neurologic findings for 48 hr following LP. Funduscopic examination was attempted in most cases, but some patients were not examined by an experienced funduscopist and some fundi could not be seen because the patient had cataracts. Agents to lower increased intracranial pressure were administered to 13 patients.

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TABLE 1

Patients Evaluated by Neurologic Examination, Lumbar Puncture, and CT

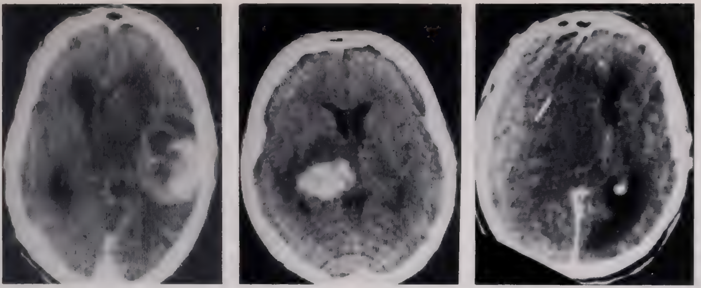
Patient		No. of days of symptoms	Neurologic findings	Pressure CSF* (mm)	Pathologic Dx by CT and other studies	Status at 48 hr
No.	Age					
1	60	2	Lethargic R hemiplegic	200	L subdural hematoma L frontal hematoma	Improved
2	43	60	Awake, confused L hemiparetic	160	R frontal hematoma	Same
3	34	3	Comatose, fixed dilated pupils	550	Subarachnoid hemorrhage	Dead†
4	77	14	Awake, confused Impaired gait	160	R subdural hygroma	Same
5	57	365	Awake	230	L cerebral tuberculoma & hydrocephalus	Same
6	28	30	Lethargic No focal deficit	130	Multiple small enhancing toxoplasmomas	Same
7	35	1	Delirious L hemiparetic	180	R temporal hematoma L caudate hematoma	Improved
8	22	4	Confused No focal deficit	210	L temporal abscess	Same
9	68	180	Lethargic No focal deficit	N/A	R parietal enhancing mass, prob. abscess	Same
10	74	180	Alert R hemiparetic	N/A	L frontal meningioma	Same
11	37	60	Confused L hemiparetic	N/A	R frontal abscess	Same
12	27	14	Alert L hemiplegic	180	R frontal enhancing mass, prob. abscess	Same
13	43	21	Confused, aphasic No motor deficit	N/A	L frontal hematoma	Improved
14	59	1	Stuporous L hemiparetic	260	L frontal abscess R cerebral infarct (old)	Same
15	9	1	Lethargic No focal deficit	210	R frontal hematoma	Improved
16	57	3	Stuporous R hemiplegic Cheyne-Stokes resp. Papilledema	N/A	L parietal abscess L thalamic abscess R frontal abscess	Improved
17	43	1	Lethargic R hemiparetic Papilledema	220	L deep cerebral hematoma	Improved
18	88	N/A	Confused R hemiparetic	N/A	L subdural hygroma	Same
19	43	14	Stuporous R hemiplegic	170	L subdural hematoma	Same‡
20	32	1	Aphasic No motor deficit	170	L temporal hematoma Ventricular hemorrhage	Same§
21	44	4	Confused No focal deficit	200	Corpus callosum glioblastoma	Same
22	67	21	Confused Apraxic gait	N/A	Chromophobe adenoma third ventricle	Improved
23	50	N/A	Confused No focal deficit	N/A	R frontal enhancing mass, probable abscess	Same
24	5	3	Alert, headache, vomiting, ataxia	N/A	Cerebellar vermis tumor ?medulloblastoma	Same
25	47	2	Confused No focal deficit	266	L thalamic hematoma	Same§
26	46	N/A	Confused L hemiparetic	420	R temporal/deep cerebral metastasis—lung primary	Same
27	50	365	Confused No focal deficit	N/A	L frontal meningioma	Same
28	76	1	Stuporous R hemiparetic	170	L frontal hematoma Ventricular hemorrhage	Improved
29	79	N/A	Lethargic R hemiplegic	N/A	L subdural hygroma	Same
30	26	1	Lethargic No focal deficit	190	L subdural hematoma	Improved
31	39	1	Lethargic L hemiparetic	N/A	Multiple ring-enhancing lesions, prob. abscesses	Improved
32	36	1	Alert L hemiparetic	190	R frontoparietal meningioma	Same
33	51	1	Lethargic No focal deficit	490	R thalamic hematoma	Same§
34	38	6 years	Vegetative state	100	L subdural hygroma with fresh blood	Same
35	61	3	Delirious, aphasic No motor deficit	200	R frontal hematoma L temporal hematoma	Improved
36	44	3	Confused R hemiparetic	N/A	L temporal infection, prob. toxoplasmoma	Same
37	44	14	Awake L hemiparetic	N/A	R parietal hematoma	Same
38	30	14	Lethargic No focal deficit	170	Multiple ring-enhancing lesions, prob. abscesses	Improved

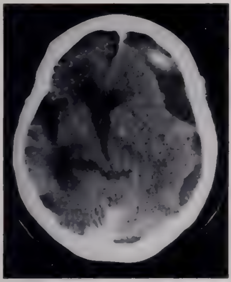
* N/A, information not available.

† Before LP was performed, patient had fixed dilated pupils, absent eye movements, and quadriplegia. Brain death was pronounced 24 hr later.

‡ Decerebrate posturing was noted immediately after CT (6 hr after LP) without changes in alertness, pupils, or eye movements. After burr hole (9 hr after LP), patient had rapid improvement.

§ Worsened in mental or neurologic function within 24 hr but returned to pre-LP status by 48 hr.





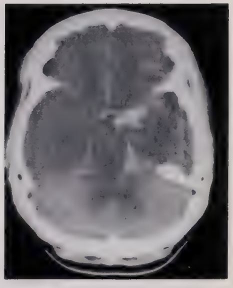


Fig. CT scans of selected patients. Slice selected to demonstrate size of lesion or effect on ventricles. **Top left** Metastatic lung cancer, patient 26. **Middle** Intracerebral hematoma, patient 25. **Right** Subdural hematoma, patient 19. **Lower left** Subdural hygroma with fresh blood, patient 34. **Lower right** Subarachnoid hemorrhage, patient 3.

Results

Thirty-eight patients with CT-documented intracranial mass lesions had LP (Tables 1–3). The lesions included hematomas, abscesses and other focal infections, subdural collections, and tumors. CT scan demonstrated or suggested mass effect in all cases. Selected scans are reproduced in the Figure. All patients but one were neurologically stable or improved 48 hr after LP. One patient who had fixed, dilated pupils and absent caloric reflexes before LP died. Three patients who were acutely ill and deteriorating at the time of LP continued to worsen afterward but returned to baseline by 48 hr. One patient with acute subdural hematoma improved following burr holes placed 9 hr after LP.

Discussion

In our series of patients with CT-documented intracranial mass lesions, LP did not adversely influence the clinical course. The only patient who died had lost brain stem reflexes prior to LP. The four other patients who deteriorated after LP were deteriorating prior to LP and returned to pre-LP status by 48 hr. Intracranial pressures were moderate in most cases (Table 1), and only two patients had papilledema.

TABLE 2
Summary of Neurologic Findings

Neurologic finding	No. of patients
Mental status	
Alert	5
Awake but confused	15
Lethargic or delirious	12
Stuporous	5
Comatose	1
Lateralizing signs	
No clear lateralization	19
Hemiparesis or hemiplegia	19

TABLE 3
Summary of Pathologic Findings Assessed by CT, Patient History, and Clinical Findings, and Biopsy or Autopsy (if available)

Pathologic finding	No. of patients
Tumor	7
Abscess	9
Infection, nonabscess	
Includes tuberculoma and suspected toxoplasmoma associated with AIDS	3
Intracerebral hematoma	11
Subarachnoid hemorrhage	1
Subdural hematoma, acute	3
Subdural hygroma, chronic	4

The results of this study agree with other reports of unselected patients with LP and intracranial masses. Lubic and Marotta (3) found one death in 401 brain tumor patients tapped at the Neurologic Institute. Masson (4) had no complications in 94 patients with tumors, including 32 infratentorial tumors. Norlen and Wickbom (5) found pneumoencephalography to be safe in 222 patients with tumors, including 82 patients with choked disk and 32 with cerebellar tumor (16 with coning of the tonsils).

Two studies claim a high risk for LP in intracranial mass; on closer examination their conclusions are unwarranted. Duffy (7) reviewed 30 patients who deteriorated after LP, but these were nonconsecutive, selected patients referred to neurosurgical centers after LP was performed elsewhere to diagnose neurologic worsening. The role of LP in subsequent deterioration was unclear. Garfield (8), in a review of intracranial abscess, felt that LP adversely affected patient outcomes. Examination of his data supports the opposite conclusion: Death rates were 32% of 140 patients with LP and 58% of 60 patients who did not have LP.

Increased cerebrospinal fluid (CSF) pressure or papilledema alone adds no risk to LP. Patients with benign intracranial hypertension (pseudotumor cerebri) and pressure over 500 mm CSF undergo diagnostic and therapeutic LP routinely. The risk of LP when increased pressure is due to life-threatening disease is unknown but is probably very small. Masson (4) reviewed 106 patients with increased pressure due to various causes. One patient died suddenly 22 hr later without signs of herniation. Korein et al (2) reviewed 129 patients, many severely ill, in whom LP showed elevated pressure: 7 of 59 without papilledema, but only 1 of 70 with papilledema, worsened after LP, suggesting that worsening was due to the underlying process, not the LP. Papilledema takes time to develop; patients without papilledema had a more fulminating process and were thus more likely to worsen whether or not LP was performed.

Experimental data are scanty. Masserman and Schaller (9) performed LP on human cadavers after raising intracranial pressure as high as 800 mm CSF but were unable to provoke block of CSF flow or appearance of herniation on contrast encephalography. Langfitt et al (10) were unable to produce CSF block in monkeys with pressures up to 40 mm Hg but easily obtained block (always at the tentorium, not the foramen magnum) by filling a supratentorial extradural balloon to 18 mm Hg. CSF removal was not performed. No experimental models have been reported in which LP caused block or herniation.

The notion that LP can cause herniation by producing a pressure gradient across the tentorial incisura appears to be conjectural. Any pressure gradient is promptly eliminated by CSF flow. If a patient herniates before LP, owing to intracranial mass, CSF could not flow to correct the pressure gradient and worsening herniation could theoretically occur. Fortunately, preexisting tentorial herniation is easily diagnosed by findings of pupillary and oculomotor fixation, quadriparesis, posturing, and respiratory changes. LP should be avoided, if possible, in such patients with clinical signs of herniation.

The data are inadequate, in this and other series, to be certain that LP with posterior fossa mass is safe. A patient could have preexisting herniation at the foramen magnum without the prominent clinical signs of tentorial block. There are, however, virtually no clinical or experimental data that LP with posterior fossa mass is unsafe.

The decision to perform LP (or any other invasive procedure) is based on risk-benefit analysis. The benefits of LP are small for most neurologic diagnoses, with the important exception of meningitis. Failure to diagnose meningitis can be fatal, as can delay in diagnosis if LP is deferred for several hours while CT results are awaited. The astute physician can differentiate between meningitis and intracranial mass in most cases, but sometimes both diagnoses must be entertained. Bacterial meningitis can produce papilledema, pupillary inequality, stupor, seizures, and focal neurologic deficits, all simulating intracranial mass. Meningitis and intracranial mass can even coexist, as in the patient rendered immunodeficient by chemotherapy for cancer metastatic to the brain. There seems to be no reason to delay LP for the purpose of obtaining CT in a patient who could have bacterial meningitis, regardless of neurologic findings of focal disease or intracranial hypertension. The dangers of LP appear minimal, the delay could be disastrous, and the decision to perform LP may be unaffected by the results of CT.

The clinical data presented in this series and cited references indicate that the risk of LP, if any, is very small when there is an intracranial mass, or when a mass cannot be ruled out. The occasional deterioration seen after LP is most likely due to worsening of the underlying condition, i.e., the very reason LP was performed.

Nonetheless, LP cannot be "proven" safe by this or any other clinical series. Such proof requires additional experimental work with artificial intracranial masses (for example, extradural balloon) and LP under controlled conditions.

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Extracorporeal Shock-Wave Lithotripsy: A Review

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Over the past ten years, there has been a radical change in the treatment of nephrolithiasis. Until the late 1970s the only effective treatment available was open surgery. By 1976, a percutaneous procedure was introduced (1). This is an invasive treatment, albeit less invasive than open surgery. It did not become widely used until the early 1980s (2), when Chaussy began the clinical application of extracorporeal shock-wave lithotripsy therapy (ESWL) for kidney stones. This was the first treatment available for nephrolithiasis not requiring incisions or endouroscopy.

The lithotripter uses shock waves which are produced outside the body by a device similar to an automobile sparkplug. The waves are transmitted through a warm water bath and through the patient's tissues, where they are focused on a fixed point (2). The patient is positioned so that the stone is at the focal point. This allows the stone to be shattered, while causing no harm to the surrounding tissue.

A typical treatment involves anesthetizing the patient, usually epidurally or by spinal methods (3), positioning the patient in the bath (accomplished by a 2-axis fluoroscopy system), and firing up to 2400 shock waves, depending on the character of the stone. The shock waves are timed with the R wave of the electrocardiogram to minimize ventricular arrhythmias that could otherwise ensue. Fluoroscopic evaluation of the patient is made at regular intervals to insure that the stone remains at the focus of the shock waves. After ESWL, the resultant fine fragments of stone are passed in the patient's urine with some discomfort over the following weeks (3). This is in contrast to open-flank surgery, in which an incision is made and renal stones are directly extracted.

Another treatment currently used is a percutaneous procedure which involves the creation and dilation of a tract from the skin of the back through the kidney and into the collecting system, where direct extraction, contact ultrasonic lithotripsy, or electrohydraulic shock-wave lithotripsy can be performed by the insertion of appropriate instruments.

Literature Review

The introduction of shock-wave therapy was based not on prior assessment by clinical trials, but rather through experimentation in laboratory models, which showed the procedure to be safe and effective. This new clinical technology has been evaluated primarily through descriptive reports of case series rather than clinical trials or other controlled studies (4). In addition, a limited number of series have been reported comparing ESWL with established treatment modalities for effectiveness, morbidity, mortality, and acceptability to patients.

The pioneering work in ESWL was by Chaussy and Schmiedt (5) in Munich, in experiments with shock waves in a number of situations. It was demonstrated that shock waves could cause the disintegration of urinary stones of varying composition (excluding cystine stones). They demonstrated minimal hemolysis when fresh blood samples were treated. Fresh isolated organs, including liver, kidney, and intestine, were also tested without deleterious effects. These results were confirmed when rats were used to evaluate the safety of the procedure. An

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in vivo model of urolithiasis, using the dog, showed that kidney stones were destroyed without any pathologic changes in either the kidney or surrounding tissue.

With this information, the authors went on to apply this therapy clinically to humans with kidney stones in 1980. Chaussy and Schmiedt reported (5) that at a three-month follow-up of all patients, 90% were stone free. These authors recommended that certain sizes of stones should not be treated, although this conclusion was not thoroughly addressed at the time.

Case Series. In an earlier study, Chaussy and Schmiedt (6) reported on a series of 550 patients receiving ESWL for treatment of upper urinary tract stones. At that time, no formal study was conducted to compare outcome with that of other treatment modalities. Despite this, the authors inferred that ESWL offers a financial advantage over surgical treatment as measured by a reduction in hospitalization time, a decrease in the inability to work, and "an avoidance of surgically induced preinvalidism."

Following this series of cases, urologists in England, Germany, and Australia began to evaluate the lithotripter without the application of clinical trails. Studies were limited to retrospective analyses of case series. A trial in England (7) selected a group of patients receiving ESWL for urolithiasis at the authors' center. These researchers describe a success rate of 80% stone-free after three months. However, this result is based on the 76% of their patients who complied with follow-up; this result may be biased if the 24% who did not comply had residual stones at a higher rate than those who did comply. The paper also notes a "very favorable" decrease in residual stone rate compared to another series in the literature reporting success rates of 80%–90% for open lithotomy.

In Germany, Schultze et al (8) described a series of patients with branched calculi treated by combination therapy with ESWL and percutaneous surgery. They claim that this therapy is less invasive and less painful than an open operation. However, there is no evaluation of patients' pain and no criteria by which pain was measured. These authors note that because no long-term follow-up data exist, there can be no proof of difference in long-term recurrence rate.

In order for ESWL to become available in the United States, the Food and Drug Administration (FDA) required that a clinical trial be performed (9). Six centers, whose representatives received training from Dr. Chaussy at Munich, undertook a noncomparative prospective study using over 2,000 patients. The report collates statistics on physical status of patients, utilizing the American Society of Anesthesiologists classification (10); age; sex; location and size of kidney stones; length of hospital stay after treatment; and status of residual stone fragments at three-month follow-up status. This was the first of such studies to consider matters other than the efficacy or safety of the treatment.

The effectiveness and safety of the ESWL treatment on renal calculi is addressed in the study, which reports that 72% of all patients' stones were pulverized by ESWL to a size less than 2 mm; 5% of patients had fragments larger than 5 mm; and 2% failed to show any disintegration upon immediate postoperative follow up. On three-month follow-up, 34% of patients had retained fragments of variable size. Seven percent of patients required additional urologic treatment before discharge. An additional 1% required intervention within three months; intervention in most cases consisted of cystoscopic stone extraction. Only 0.6% of the patients required some form of open incisional operation.

Urinary infections, or possible urinary infections based on symptomatology, occurred in 7.2% at admission time. Only 5% of patients were symptomatic at time of discharge. The study did not determine which of the infections at discharge were new and which represented a reduction in previous infections.

Nonurologic complications totaled 7%, including 1% due to anesthesia complications (the accepted standard risk of all anesthesia), and four deaths, two due to cerebrovascular accidents and hypertension, and two believed to be due to unrelated diseases.

The researchers also were able to draw a number of applicable correlations from the analysis of their data. They found a positive correlation between the size of the stone treated and the level of post-treatment pain. Pain, in most cases, is due to passage of stones and fragments through the ureter. The authors report that patients with stones less than 1 cm in size more often reported no pain or less intense pain on discharge of the stone than those with stones larger than 1 cm, and that in addition, patients who had stones larger than 1 cm were significantly more likely to require narcotics for pain control. That patients with larger stones required more shocks to complete the treatment was also expressed, but no correlation was drawn between the number of shocks and postprocedural pain, despite the fact that both these factors were shown to be related to stone size. It was shown that significantly more patients had an overall increase in pain level from the time of admission to the time of discharge; however, stone size was not controlled for in this association, despite the result that postprocedure pain was related to stone size. From the results of these 2,000 treatments in the United States and over 8,000 treatments worldwide, the FDA approved ESWL for use in nephrolithiasis and judged it to be both safe and effective.

Evaluation by Comparison with Other Therapeutic Procedures. The safety and efficacy of ESWL may be established through a comparison of outcome with outcome of existing treatments for urolithiasis. This is in contrast to simple noncomparative analysis of outcome of ESWL, without regard to outcomes of other treatment modalities. The following studies are the only ones to date which utilize the comparative approach to realizing the inherent advantages and limitations of ESWL.

In March 1986, Charig, Webb, Payne, and Wickham (11) of the London Stone Centre presented a series of 1,052 patients with urinary calculi, of whom 350 underwent open surgery from 1972 to 1980, 350 underwent percutaneous nephrolithotomy from 1980 to 1985, and 352 underwent ESWL in 1985. These patients were examined retrospectively in an unmatched fashion. Patient groups were selected by an unspecified mechanism and were stratified into two categories by stone size. The groups were compared with regard to cost of treatments, mortality, and success rate of treatments as defined by absence of stones or the reduction of stones to particles less than 2 mm in size after three months. Costs in terms of hospital days were presented as averages: 16.1 days for the surgical groups, 7.0 days for the percutaneous group, and 3.7 days for the ESWL group. Mortality was minimal in the three groups: 0.9% for the surgical group, 0.7% for the percutaneous group, and 0% for the ESWL group. The authors further stated that overall success rate was superior in the ESWL group.

In another series reported by Bush, Gibbons, Lewis, and Brannen in July 1986 (12), a comparison of ESWL and percutaneous stone procedures was made retrospectively, using 300 ESWL patients and 300 percutaneous patients compared in an unmatched fashion. The percutaneous patients had received treatment at that particular institution prior to the installation of a lithotripter in May 1985.

The actual parameters for analysis in the Bush study were hospital stay, return to work, and postprocedure complications. Data are presented for the 300 percutaneous patients and the 300 ESWL patients as well as a group of 100 additional surgical lithotomy patients. The authors concluded that morbidity is minimal in ESWL as compared with percutaneous and surgical methods. Hospital-stay averages were 10.8 days for the surgical, 5.5 days for the percutaneous, and 1 day for the ESWL group. Return-to-work averages were 3.8 weeks, 1–3 weeks, and less than one week for the three groups..

Summary

ESWL has changed the treatment of nephrolithiasis significantly over the last ten years. In view of the fact that many stone centers today perform few surgical lithotomies, the emergent ESWL treatment has received adequate assessment with regard to efficacy, safety, and patient satisfaction. ESWL case series have addressed questions such as stone-free success rate, complications of ESWL, and levels of post-treatment pain. Nonetheless, case series do not provide controls for these parameters using other stone removal procedures as standards. A limited number of studies have compared ESWL to lithotomy or percutaneous procedures. These have shown ESWL to be superior in terms of success rate, mortality, morbidity, and cost of treatment.

Unfortunately, these studies have been retrospective and may not satisfy those who demand a rigorous evaluation of ESWL. An idealized assessment of ESWL requires the use of randomized clinical trials; none have been performed to date, largely because of ethical objections. A realistic solution to this dilemma involves the use of a historical controlled clinical trial or nonrandomized prospective study to fully evaluate this promising new technology.

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Mediastinoscopy: Its Changing Role

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Abstract

A total of 426 cases of mediastinoscopy performed at Bronx VA Medical Center between 1965 and 1985 have been reviewed. The initial indication for this procedure was a routine screening for bronchogenic carcinoma assessing operability as well as diagnosing the various pathologies involving the mediastinal nodes. A few striking trends are noted in this 21-year period: a sharp decline in the diagnosis of sarcoidosis since 1974; decreased numbers of "no tissue biopsy"; and increased incidence of positive nodes from bronchogenic carcinoma since the late 1970s. These trends coincided with new developments in related medical fields and changing concepts of mediastinoscopy. At present, the role of mediastinoscopy in our institution is limited to establishing histologic staging in highly selected cases only, rather than for screening the cases.

It has been more than a quarter-century since the first report of mediastinoscopy by Carlens was published in 1959 (1). The initial purpose of this procedure was to assess the extent of metastasis of bronchogenic carcinoma to the mediastinal lymph nodes (1). Presence of positive nodes was considered a contraindication for surgery (2). Since then, the indications for mediastinoscopy have expanded to include diagnostic and therapeutic studies of nonmalignant disease (3, 4). At the same time, its values, especially in assessing the meaning of the positive node, has become a focus of intensive discussion (5–8). As experience accumulated, however, the indications for mediastinoscopy have also been discussed, heavily influenced by new developments in related medical fields, mainly transbronchial biopsy with flexible bronchoscope (9, 10) and computerized-tomography (CT) scan of the chest with contrast (11) for the past few years.

Review of our experience of mediastinoscopy for the past 21 years clearly exhibits these trends.

Materials

Mediastinoscopy was performed in 426 patients at Bronx VA Medical Center between January 1, 1965 and December 31, 1985. Pathology reports, operative reports, and tumor registry of these patients were reviewed. The primary purpose of the procedure for all cases was diagnostic, except for a few cases in which the procedure had therapeutic as well as diagnostic aims. These 426 cases were analyzed for (a) annual case load and (b) yield of pathology, in order to evaluate any existing trends. The series was divided into three 7-year periods for analytical purposes. Two additional types of information were obtained to help analyze the data. One was the number of cases of the granulomatous disease (namely sarcoidosis), which was diagnosed by bronchoscopy with flexible scope, with or without transbronchial biopsy. The second was the incidence of mediastinal node involvement (N2) (12) at the time of the thoracotomy. When the status of nodal involvement was not specified, the case was classified as NX.

Results

Annual Case Load

A significant decrease in annual case load occurred around 1979. During the first and second periods (1965–1978), the number of cases

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TABLE 1
Yearly Case Load

Period	No.	Cases per year
1965–1971	187	26.7
1972–1978	180	25.7
1979–1985	59	8.4
Total	426	20.3

TABLE 2
Yield of Pathology

Positive	147
Metastasis from lung	107
Granuloma	30
Others	10
Negative	243
No biopsy	36
Total	426

per year was fairly stable. A total of 367 cases were performed in this 14-year period, with an average of 26 cases per year. Only 59 cases were done for the next 7 years, with an average of 8.4 cases per year (Table 1, Fig. 1).

Yield of Pathology

Overall Results. Positive tissue diagnosis (all pathologies) was obtained in 147 of 390 cases on which biopsies were taken. In the remaining 243 cases, no tissue diagnosis was established. An additional 36 cases had no tissue biopsy. Thus, yield of pathology was 147 of 426 (34.5%). Of 147 patients who had positive tissue diagnosis, 107 were found to have metastatic bronchogenic carcinoma. Granulomatous disease (mainly sarcoidosis), the next most common diagnosis, was found in 30 cases. Ten cases had various diagnoses, including metastatic renal cell carcinoma and benign cyst (Table 2).

Cases of "No Biopsy." Thirty-two of thirty-six cases in this category occurred in the first 7 years of this series, when a total of 187 mediastinoscopies were performed (incidence 17%). Only 4 cases were noted among 239 in the next two periods (incidence 1.7%) (Fig. 2, Table 3). These 32 cases were further analyzed to determine whether the reason no tissue biopsy was obtained was a limited disease process or other factors. Ten patients did not receive any further surgical procedures. Twenty-one patients underwent thoracotomy. Exploratory thoracotomy only was performed in 7 patients, who had unresectable bronchogenic carcinoma. Thirteen patients underwent resection—4 lobectomy and 9 pneumonectomy (including 1 for benign and 1 for metastatic melanoma). In one additional case, benign pathology was found by exploratory thoracotomy.

Granulomatous Disease. In the first period (1965–1971), 18 of 187 cases had a diagnosis of granulomatous disease; in the second period, 11 of 180, and only one of 59 cases in the last period.

When this was further analyzed (Fig. 3), 28 of 30 cases of granulomatous disease (mainly noncaseating, compatible with sarcoidosis) were diagnosed between 1967 and 1973 (incidence 9.3%). Only 2 cases were reported after 1974 (incidence 1.2%).

In contrast to this trend, the principal method of diagnosing the granulomatous disease was replaced by flexible bronchoscopy, which was introduced to our institution in 1973. Transbronchial biopsy technique was introduced in 1975 (Table 4).

Metastatic Bronchogenic Carcinoma. In the first 7 years (1965–1971), 40 of 187 patients were found to have metastases from bronchogenic carcinoma (21%). In the next 7 years (1972–1978), 41 of 180 (23%) were positive. In the last 7-year period (1979–1985), 26 of 59 (44%) were positive (Table 5).

Entire Series. Analysis of the entire series of mediastinal node involvement at the time of thoracotomy (N2), either with or without mediastinoscopy, yielded the following results. In a group

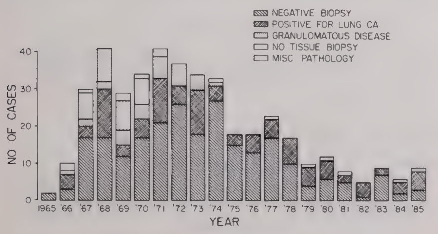

Fig. 1. Summary of all cases.

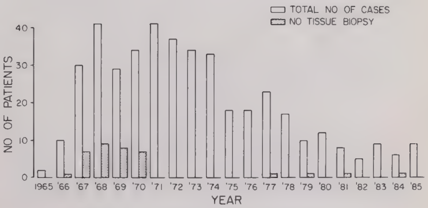

Fig. 2. Trends in no tissue biopsy.

TABLE 3

Cases of No Biopsy

Period	Total no.	No. biopsy no. (%)
1965–1971	187	32 (17%)
1972–1978	180	1 (0.6%)
1979–1985	59	3 (5%)
Total	426	36 (8.4%)

TABLE 4

Granulomatous Disease, Diagnosed by Flexible Scope

Year	No.	Year	No.
1975	1	1980	7
1976	2	1981	2
1977	2	1982	2
1978	2	1983	1
1979	5	1984	3
		1985	6

TABLE 5

Metastasis from Lung Carcinoma

Period	Total no.	Positive no. (%)
1965–1971	187	40 (21)
1972–1978	180	41 (23)
1979–1985	59	26 (44)
Total	426	107 (25)

without mediastinoscopy, 15 of 84 cases (18%) of known N stage were N2, and 27 of 96 (28%) were N2 in a group with mediastinoscopy. (Results of a series between 1979 and 1985 will be discussed later.)

Discussion

The original purpose of mediastinoscopy was to assess whether the mediastinal node was involved by the metastasis from bronchogenic carcinoma. Any patients who had positive nodes were considered inoperable and excluded from a thoracotomy (2, 13). This approach resulted in improved resectability (14) and decreased incidence of exploratory thoracotomy for unresectable carcinoma, which is associated with poor prognosis (15). Some authors further advocated that exclusion of such patients would not alter overall 5-year survival rate (14). With the accumulation of experience, however, this belief has been challenged (7). As a result, newer concepts with regard to patients with positive nodes developed. A selected group of the patients with limited metastasis were no longer considered inoperable (16, 17). This group includes ipsilateral single-node metastasis (6, 17) and intranodal metastasis (18). At the same time, more selective, rather than routine, use of mediastinoscopy was advocated (19).

Meanwhile, new developments in related medical fields began to affect the practice of mediastinoscopy. The two most important developments were transbronchial biopsy with flexible bronchoscope and CT scan of the chest, especially with contrast. The effects of these changes were clearly reflected in this series.

Decline in the number of cases of granulomatous disease is a direct effect of development of the flexible bronchoscope and transbronchial biopsy technique. Mediastinoscopy, with or without scalene node biopsy, used to be the technique of choice to obtain tissue diagnosis for this disease (3), but this new development, which was introduced to our institution in the early 1970s, essentially eliminated the need for mediastinoscopy for diagnostic purpose. Two factors (the evolving concept of mediastinoscopy, and the development of CT scan with contrast) strongly affected selection of the cases for mediastinoscopy and the results. Until 1977 mediastinoscopy was performed for almost all cases of bronchogenic carcinoma as a part of the preoperative screening procedure prior to thoracotomy. The few exceptions were usually the cases for pure palliation, such as debulking or lobectomy for obstructive

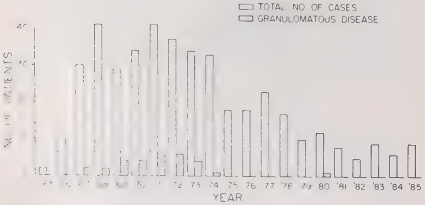

Fig. 3. Trends in granulomatous disease.

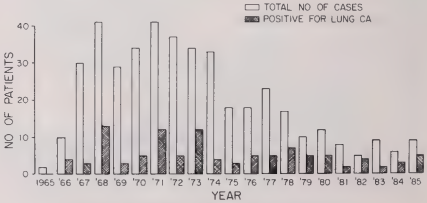

Fig. 4. Metastasis from lung carcinoma.

pneumonia. Thus, the incidence of negative biopsy was high. A new approach (i.e., selective mediastinoscopy) was gradually adapted around 1978. The cases were selected by clinical and x-ray findings, including tomogram (20, 21), and mediastinoscopy was performed only in suspicious cases. This approach resulted in a decline of total cases as well as an increased incidence of positive biopsy (Table 5).

In 1982, CT scan of the chest with contrast became operational in our institution as a part of preoperative evaluation of the mediastinum for the patients with bronchogenic carcinoma. If the CT scan failed to show suspicious node, thoracotomy was performed without mediastinoscopy. The same trends continued (Fig. 4).

The feasibility of selective mediastinoscopy was checked using two parameters: the incidence of exploratory thoracotomy and the incidence of mediastinal node involvement (N2) at the time of thoracotomy.

A series between 1979 and 1985 was further analyzed in these two areas since systemic intentional selective mediastinoscopy was performed mainly in this period. A total of 55 thoracotomies were performed without mediastinoscopy in this period, 2 of which were exploratory; thus the incidence of exploratory thoracotomy was 3.6%. Among 22 thoracotomies following mediastinoscopy, 2 were exploratory only (9%). The incidence of N2 lesions in the group without mediastinoscopy was 14.3% (6 of 42 cases with definite nodal classification); in the mediastinoscopy group, 5 of 17 cases with definite nodal classification (29.4%) had N2 lesions. No undesirable effects due to selective mediastinoscopy were noted in these two important areas.

The high numbers of "no tissue biopsy" cases in the first 6 years may be related to surgeons' experience. The high incidence of exploratory thoracotomy in this group is suggestive of incomplete exploration of the entire mediastinum. Meticulous and skillful techniques are required for thorough mediastinoscopy.

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Clinical Utility of Nondrug Therapy for Hypertension

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Abstract

We assessed the effectiveness and practicality of lowering blood pressure in an unselected (self-selected) hypertensive patient population in a clinic, utilizing a multimodal nonpharmacologic protocol. The protocol had four parts: "de-salting," weight reduction, relaxation techniques, and increased physical activity. Patients participated in a 20-week protocol that included physician visits and group teaching sessions. A low-calorie, 1-gm sodium diet (either formula or food) was used during the "de-salting" phase. Prescription modifications in diet and antihypertensive medication were made in response to changes in blood pressure levels. Although previous studies have examined the effects of low sodium diets on blood pressure, it is difficult to compare our results with theirs for several reasons. Our study used formula diets in addition to "no added salt" food diets. We attempted to reduce caloric intake; earlier studies did not. We did not obtain urinary sodium measurements to gauge intake; other studies did. We were not attempting to duplicate a controlled trial isolating one intervention.

Of the 46 patients who completed the program, 27 were normotensive at exit; of these, 24 needed no medication. For the group as a whole, there were significant declines in weight ($p < .01$), systolic blood pressure ($p < .01$), diastolic blood pressure ($p < .01$), and number of medications used ($p < 0.01$). The effectiveness of the nondrug regimen and the ease of implementation of the program make this a viable alternative to drug therapy in the mild-to-moderate hypertensive population.

There is growing evidence that nonpharmacologic approaches to controlling blood pressure represent viable therapeutic alternatives in mild-to-moderate hypertensives (1–3). Sodium restriction (4–9), weight reduction (10–13), relaxation therapies (14–17), and increased physical activity (18–22) have been shown to exert beneficial effects on blood pressure. Further, with each of these modalities, it has been possible to reduce or discontinue antihypertensive medication.

Three factors influence the physician's decision to treat a patient with nondrug therapy: side effects of medication, noncompliance with drug regimens, and patient's desire to participate actively in their own health care. Several studies have raised concerns about the relationship of antihypertensive drug therapy both to cardiovascular morbidity and mortality (23) and to noncardiovascular disease (24). Further, it is well documented (25–30) that antihypertensive medication can induce undesirable alterations in serum electrolyte and lipid levels. The quality-of-life changes (31–34), though more subtle, are no less disturbing.

These negative changes in physiologic and psychological status, when combined with the asymptomatic state of most untreated mild hypertensive patients, probably contribute importantly to the major problem of noncompliance with antihypertensive drug regimens (35–37). Finally, frequent negative side-effects, poor com-

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pliance, and the growing desire of medical consumers to participate actively in their own care make the option of nonpharmacologic treatment valuable for both patient and physician.

Although several studies have examined the combined effects of sodium restriction and weight loss (10, 12), we identified only one previous study (38) that explored the simultaneous impact of weight reduction, sodium restriction, increased physical activity, and relaxation therapy on blood pressure. We were interested in both the effectiveness and the practicality of using a multimodal approach to nondrug therapy in an unselected patient group. We hope to show that a short but intense exposure to structured suggestions about major changes in these four areas, with peer-group pressure and support, could positively effect both short-term and long-term responses of blood pressure.

Participants and Methods

All of the first two cohorts of patients (55) who were enrolled in our program were self-referred. Participants were accepted whether they were on anti-hypertensive medications or not. Prior to the initial cardiovascular examination, individuals with unconfirmed hypertension were screened with three separate blood pressure (BP) measurements and were considered eligible if the mean of these recordings was greater than 140/90 mmHg. Individuals were excluded if they had (a) secondary HTN of known origin; (b) stroke, myocardial infarction, congestive heart failure, or renal failure within the preceding six months; (c) manic-depressive illness treated with lithium; (d) tricyclic antidepressant therapy; or (e) inability to comprehend the program. Candidates who had had coronary artery bypass surgery and those taking antihypertensive agents for the treatment of other medical conditions (diuretics for congestive heart failure, B-blockers for angina, migraine, or post-MI prophylaxis) were included at the discretion of the examining physician. Age, sex, duration of diagnosed hypertension (HTN), and duration of HTN therapy were not used as exclusionary criteria.

Prospective patients attended a group orientation during which the rationale and details of the protocol were explained. Those interested filled out a medical history form which was reviewed by a registered nurse. Appropriate candidates were then scheduled for a cardiovascular examination, which included three sitting and two standing blood pressures; sitting and standing pulse rate readings; examination of the optic fundi, heart, lungs, abdomen, peripheral blood vessels, thyroid, extremities, and neurologic status; urinalysis; hemogram; thyroid profile; serum chemistries; serum lipoproteins; EKG; and, when indicated, an EKG stress test. At a subsequent session, the results of these examinations were reviewed with each patient by a physician, and a final decision about inclusion in the program was made. Patients gave written informed consent. The protocol had been approved by our local Institutional Review Board.

Patients received instruction on measuring and recording home blood pressure levels on their own machines. These devices were calibrated to the unit used in the clinic. For each of the next four weeks patients were seen by their clinic physician and attended a series of group teaching sessions. During the first physician visit, home BP records were reviewed. Patients were then assigned either a low-calorie, 1 gm sodium formula (supplied by the Sandoz Nutrition Corporation) or a low-calorie, 1 gm sodium food diet. All diuretics were discontinued.

As part of their diet instructions, patients were asked not to use alcohol, but no formal attempt to quantify ongoing alcohol use was made. Similarly, no attempt was made to curtail or monitor tobacco use in the four patients who smoked.

During subsequent physician visits, caloric restriction was either maintained or modified based on changes in blood pressure, not weight. No patient stayed on the formula diet for longer than two consecutive weeks; if continued equivalent caloric restriction was required, the diets were changed to the low-calorie food regimen. Similarly, reductions or terminations of other antihypertensive medications were made at the physician's discretion, on the basis of BP level. If subsequently necessary, physicians could increase or restart medication. Blood pressure, weight, home BP records, and any problems that had arisen during the preceding week were reviewed.

Between the third and fifth weeks, depending on BP and caloric intake, patients were given an individualized physical activity prescription based on age, medical history, and previous level of conditioning. The exercise level was gradually increased during the protocol toward a target of three sessions per week, each consuming 300 kcal.

The teaching sessions included basic information on nutrition (what are calories, fat, carbohydrates, protein, salt: what are their sources; what are their roles in the body), an introduction to relaxation therapy and the distribution of a brief relaxation tape cassette for home use, an introduction to programs of increased physical activity and their effect on hypertension, and a review of relaxation therapy and the teaching of hand warming. Patients received additional instruction in these areas on an individual, as-needed basis.

After week five and until the conclusion of the protocol (maximum of 20 weeks), patients were seen weekly or biweekly at the discretion of their physicians. Changes in diet, exercise, and medication were made as described earlier. At any point in the program when BP became normal off medication, a decision could be made to place the patient on a maintenance diet. The caloric content of the maintenance diets was calculated on the basis of desired weight, current weight, height, and activity level. All maintenance diets contained 2–5 gm/day sodium and the U.S. RDA for all other minerals.

At 20 weeks, or earlier if normalization of BP without medication was successful, all the laboratory studies were repeated, and the results were reviewed with the patient. A triage decision was then made for follow-up care. "Successes"—those patients who were normotensive without medication—were offered a monthly maintenance clinic, where weight and BP were checked. These graduates had the option of returning at any time for refresher courses by attending any of the teaching sessions. Patients who still required medication to control BP had the option of returning to their private physicians or, if they had no such physician, of having their medications and BP monitored through the clinic.

In this study, patients were classified as "obese" at entry if they were more than 20% above their ideal body weight; BP was considered "controlled" if it was less than or equal to 140 ± 5/90 ± 5 mmHg.

Of the first 55 patients who entered the program, nine dropped out before completion of the protocol. This report examines the results for the remaining 46 patients. The data were analyzed using the *t*-test, analysis of variance, and chi-square methods.

TABLE 1
Patient Demographics

Characteristic	Measurement
Age, yrs ± SD	51 ± 8
Male	26 (57%)
Female	20 (43%)
White	37 (80%)
Black	9 (20%)
>20% over ideal body weight	25 (54%)
Initial systolic BP, mmHg ± SD	147 ± 21
Initial diastolic BP, mmHg ± SD	94 ± 13
No. of pts taking antihypertensives	
no medication	12 (26%)*
1 medication	14 (30%)
2 medications	18 (39%)
3+ medications	2 (4%)

* Includes 4 patients who self-discontinued antihypertensive medication within 2 wk of start of program.

Results

The majority of the participants were white and middle-aged and had mild-to-moderate hypertension treated with one or two drugs (Table 1). Overall, of the 46 patients who completed the program, 27 left with controlled BP (59%); of these 27, 24 (52% of 46 patients) were not taking medication. Of the 24, eight had begun the program taking no medications, eight taking one drug, and eight taking two drugs. Thirteen of the 24 (54%) had begun the program obese, and 11 (46%) had begun the program nonobese.

For the group as a whole (Table 2), over the course of the study there was a significant decline in weight ($p < 0.01$), systolic blood pressure ($p < 0.01$), diastolic blood pressure ($p < 0.01$), and

TABLE 2
Change in Weight and Blood Pressure (BP) in Obese and Nonobese Participants

	Weight (kg ± SD)		Systolic BP (mmHg ± SD)		Diastolic BP (mmHg ± SD)	
	initial	final	initial	final	initial	final
Total pt group	91 ± 21	81 ± 18*	147 ± 21	141 ± 22*	94 ± 13	90 ± 10*
Obese subgroup	104 ± 18	92 ± 16*	147 ± 23	140 ± 23†	95 ± 15	91 ± 11
Nonobese subgroup	75 ± 12	68 ± 11*	147 ± 19	143 ± 22	92 ± 10	87 ± 9‡

* $p < 0.01$
† $p < 0.03$
‡ $p < 0.02$

TABLE 3

Initial and Final Blood Pressure (BP) and Medication (Meds) Status

		Initial status				Final status		
Group	No. pts	BP	meds	BP (mmHg ± SD)	No. pts	BP	meds	BP (mmHg ± SD)
I	4	Norm	0	133/83 ± 9/5	4	Norm	0	127/83 ± 10/8
II	15	Norm	+	129/85 ± 10/7	12	Norm	0	130/84 ± 8/5
					1	Hyp	0	132/100 ± 0/0
					2	Hyp	+	145/99 ± 5/1
III	21	Hyp	+	161/101 ± 19/13	4	Norm	0	141/89 ± 2/7
					3	Norm	+	132/83 ± 4/8
					8	Hyp	0	154/95 ± 8/4
					6	Hyp	+	175/101 ± 35/13
IV	6	Hyp	0	150/99 ± 6/6	4	Norm	0	119/81 ± 8/3
					2	Hyp	0	147/97 ± 13/1

Norm, normotensive; Hyp, hypertensive. Medication status: 0, none; +, one or more.

number of medications used ($p < 0.01$, data not shown). Within-group comparisons showed that the obese patients had a significant fall in weight ($p < 0.01$), systolic BP ($p < 0.03$), and number of medications used ($p < 0.01$). For the nonobese patients, weight ($p < 0.01$), diastolic BP ($p < 0.02$), and number of medications used ($p < 0.01$) were all reduced significantly. Between-group comparisons showed that the obese group had a greater weight loss over the course of the study ($p < 0.001$) than the nonobese group. The obese group did not, however, have a greater fall in either systolic or diastolic BP over the course of the study. There were also no significant differences in initial systolic or diastolic BP.

Patients were accepted into the study whether or not they were taking antihypertensive medication at entry. The prestudy-poststudy trends reflected in Table 2 do not take this heterogeneity on entry status into account. Thus, some patients may have been normotensive at entry because of medication and left the study normotensive without medication, not experiencing a significant change in their actual BP readings.

The 46 patients were classified into four subgroups (Table 3) based on initial degree of blood pressure control (normotensive vs hypertensive) and initial medication status (medication vs no medication). Group I patients had recently documented hypertension and/or a history of borderline hypertension with a strong family history of cardiovascular disease. The 15 patients in Group II began the study normotensive with medication (four patients taking one drug, 11 taking two drugs). All four patients initially taking one drug and eight of the 11 initially taking two drugs finished normotensive on no medication. Of the remaining three patients initially taking two drugs, one finished the protocol hypertensive without drugs, and two left hypertensive with one drug.

The 21 patients in Group III were hypertensive when they began the program despite taking antihypertensive medications. Of these, 7 were normotensive at exit, 4 taking no drugs, 3 taking medication. One of these three entered taking three drugs and left taking two, and another entered taking two drugs and left taking one. The third patient both entered and exited taking one drug. Fourteen of the 21 patients in Group III were still hypertensive at exit; 8 were taking no medictions and 6 continued to take drugs. Five of these 6 were taking fewer medications at exit. At entry, these 14 patients had the highest blood pressure levels of the two cohorts (mean ± SD), despite their antihypertensive drugs, and were at the upper end of the scale for moderate hypertension. Group IV consists of six patients who began the study hypertensive with no drug therapy.

Those patients who left the program with their blood pressure controlled had a greater weight loss over the course of the study than those whose blood pressure was not controlled at exit ($p < 0.05$). Those patients controlled at exit did not have a statistically greater change in their systolic or diastolic BP than those who left uncontrolled, though there were trends in this direction (9 mmHg vs 2 mmHg mean fall for systolic, 6 mmHg vs 2 mmHg mean fall for diastolic pressure).

Discussion

Although previous studies (5–9) have examined the effects of low sodium diets on blood pressure, it is difficult to compare our results with theirs for several reasons. First, these studies used no formula diets, instead employing what might be called "no added salt" food diets. Second, no attempt was made to reduce caloric intake in these studies, while the current study did. Third, urinary sodium measurements, used as checks of sodium intake in the other studies, were not obtained in our study. The success of these earlier studies prompted us to include salt restriction as one of the modalities in our protocol, but we were not attempting to duplicate a controlled trial isolating one intervention.

This program was designed to evaluate a multimodal approach to the nonpharmacologic treatment of hypertension and to estimate its applicability to a routine clinical setting. Our past experience with patients (12, 39) has shown that in mild-to-moderate hypertensives, excessive salt intake and obesity are primary factors in the elevated blood pressure levels. Because of the reported positive effects of the other nondrug modalities—increased physical activity and relaxation techniques—we also incorporated these into our program.

Although the roles of sodium, calcium, and other electrolytes in the development of hypertension are somewhat controversial (40–42), we based our first step of "de-salting" our patients on the principle that salt consumption and retention is a substantial factor in a number of hypertensive individuals. Once the patient has been "de-salted," it is important that he or she be assigned a balanced diet containing all the essential electrolytes with maintenance levels of 2–5 gm sodium and 1 gm calcium.

Because of our previous success with the low-calorie formula diet (43, 44), we used this approach in this current study. Our preliminary experience indicates that "de-salting" is achieved more easily with the formula diet than with the low-calorie food diet. With this in mind, we have defined three settings in which this approach would be helpful to the patient: (a) short-term prescription during the initial, intensive nondrug protocol, (b) reintroduction for "de-salting" of patients who have regressed, (c) an established protocol of combined formula and food diet which allows the patient to liberalize the food source of the maintenance level of sodium and calories.

Of the other three parameters in this protocol—weight reduction, increased physical activity, and relaxation therapy—weight is the easiest to quantify. Our data, therefore, focus on this variable and its effect on blood pressure and medication levels. The study population was heterogeneous as defined by weight (Table 1). Although, as expected, the obese patients had a greater reduction in weight, they did not have a greater decrease in blood pressure, and their representation in the "successful" group (normotensive without medication) was identical to their proportion in the sample as a whole (54%). Thus, although obese patients profited from our intervention, they did not do so disproportionately. For the nonobese patients as well, weight loss was related significantly to achievement of a normotensive state and was a clear benefit of the program. Of further interest is that blood pressure could be normalized with quite modest weight reductions. Even in obese patients, 3–4.5 kg losses were frequently sufficient to bring blood pressure under control. The concept that patients may have a critical weight at which normotension can be achieved and that this weight is not necessarily ideal body weight is important. It defines reasonable and attainable goals for both physician and patient and clearly separates weight loss for the purpose of blood pressure control from weight loss for other health or esthetic purposes.

Our experimental design does not allow us to comment on the potentially independent contributions of exercise and relaxation therapy. Short of randomly withholding one or another of our interventions or more clearly separating their onset in time, we could not have validly explored this issue. Moreover, our purpose was to estimate the combined power of these modalities when utilized in a single clinical intervention. With this objective in mind, we incorporated programs of physical activity and relaxation therapy which provided simple, usable techniques for home use.

Given the pragmatic goal of our program, that more than half of our patients were able to leave the study with normal blood pressure levels with no drug intervention is a striking result. The heterogeneity of this successful group (54% obese, 46% nonobese at entry; 33% each taking 0, 1, or 2 drugs at entry) offers support to the general applicability of such an intervention to an unscreened population of mild-to-moderate hypertensives. Considering the diversity of the study group, it is of further note that the entire group experienced statistically significant reductions in weight, systolic blood pressure, diastolic blood pressure, and medication use (Table 2).

A fuller appreciation of the beneficial impact of the study is gained from the data in Table 3. In addition to the patients who left the study normotensive and unmedicated, a number of participants might be labelled "partial successes." Patients who began the study hypertensive and medicated and finished still medicated but normotensive improved their cardiovascular risk status by bringing their blood pressure under control. Of the patients in Group III who remained hypertensive at exit and who subsequently were referred to drug therapy, 12 had their medications either reduced or discontinued while on the study without a significant rise in blood pressure.

All of the 46 patients completed this protocol six to eight months ago. Because of this short follow-up period, we cannot comment on the long-term efficacy of our intervention. Based on studies of weight loss (12, 46, 47) which suggest that alterations in life-style are difficult to maintain, especially without ongoing support and motivation, we believe that brief follow-up sessions should be scheduled each month for the first year. As of August 1, 1985, of the 20 patients who have returned for follow-up and who were normotensive and unmedicated at exit, all have remained off drugs; five patients have shown trends of increased blood pressure levels and have renewed active participation in the program.

The ease with which the protocol was implemented deserves comment. The patient's motivation is critical to the success of the program. The willingness to participate in the educational sessions, to appear regularly for monitoring, and to implement life-style changes is the key to achieving nonpharmacologic control of blood pressure. Patient motivation can be dramatically modulated by staff attitudes; committed, enthusiastic medical and paramedical personnel are vital to insuring compliance.

Much of the intervention can be rendered by nonphysicians. While a smoothly functioning health-care team with clearly articulated responsibilities is necessary, the program is not inordinately time-consuming. Teaching sessions, dietary counseling, and physician follow-up could easily be incorporated into most private offices without additional personnel.

In summary, our results demonstrate that for a group of mild-to-moderate hypertensives, a combined-modality approach utilizing sodium restriction, weight reduction, aerobic activity, and relaxation techniques may be highly effective in normalizing blood pressure. After completion of a 20-week protocol, over half of our patients were free of medication and able to enter a maintenance program. Such a program seems applicable especially to those patients motivated to embrace lifestyle changes among the heterogeneous population seeking treatent from primary care physicians. A physician can, with minimal additional time and with trained personnel, offer this approach to patients as an alternative to drug therapy.

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An Unusual Concurrence of Myotonia Congenita and Wilson's Disease

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Wilson's hepatolenticular degeneration has been associated with a variety of systemic metabolic derangements, both as a direct result of copper deposition in tissues and as a complicating result of organ failure. Thus the classic extrapyramidal and hepatic manifestations, as well as coagulopathy (1), glucose intolerance (2), hemolytic anemia (3), Fanconi syndrome (4) with amino aciduria (5), renal rickets (6), thrombocytopenia (1), and hypoparathyroidism with symptomatic hypocalcemia (7) have been reported. Occasionally the concurrence of rare diseases raises the question of some underlying pathophysiologic relationship. We report an unusual concurrence of rare diseases, myotonia congenita, recessive type, and Wilson's disease.

Case Report

A 19-year-old Argentinian man was admitted to The Mount Sinai Hospital after suffering two episodes of hematemesis. In addition to the precipitating cause for admission, his major complaints were inability to walk, tremor, drooling, and personality change which preceded the other symptoms and began eighteen months prior to admission. There had been no prior history of hematemesis or jaundice.

The patient's birth history was normal, and he achieved normal developmental milestones. Since childhood he had been described as muscular and "tense." At age 8 years he had several episodes of epistaxis and gingival bleeding. The patient reported always bleeding for prolonged periods when cut. At this age his family noted that he had difficulty getting up from a sitting position and stiffness when initiating activities such as writing and walking. He experienced occasional muscle cramping. He reported that he did not have pain, but rather mostly tension in his muscles. This stiffness did not worsen in cold, but improved with continued effort. He was always athletic in appearance but not agile. These symptoms improved when he underwent oral quinine therapy temporarily.

Eighteen months prior to admission he became depressed about his breakup with a girlfriend. He took antidepressant medication for a short period. No neuroleptic usage was reported. At that time his family noted intermittent drooling of saliva, dysphagia, dysarthria, and a change in personality to an overoptimistic attitude. He nevertheless finished a second year of college. Ten months prior to admission, he noted gait difficulty and described his feet as becoming glued to the floor. Dysphagia and drooling worsened. His affect became continuously euphoric, and he experienced spasms of laughter. At six months prior to admission, he began falling backward. This symptom progressed over two months to an inability to stand. He developed tremor in both upper extremities, and was essentially bedridden. In addition to these symptoms, he reported intermittent abdominal pain over two years.

The patient had been taking aspirin daily on the advice of a physician. He had no history of alcohol or drug abuse. The patient had one brother ten years older who was smaller in stature. Both parents and his brother were in good physical health with no history of liver or neurologic disease. The parents were reported to be distant cousins from a village in central Spain

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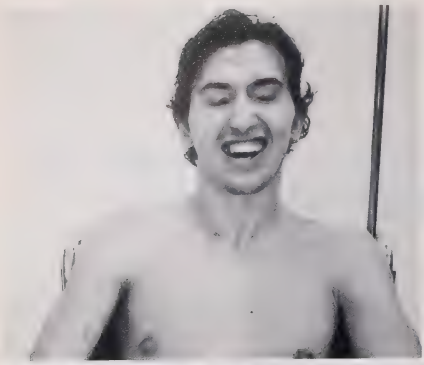


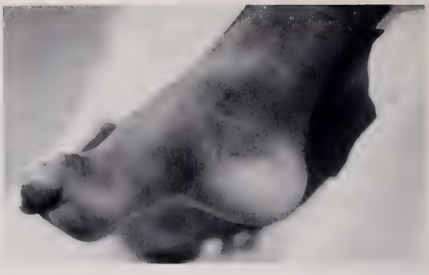
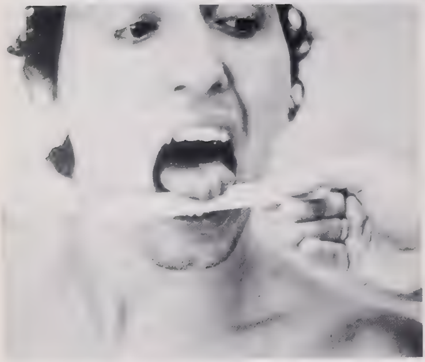


Fig. 1. Above left Patient's characteristic appearance of continuous fixed smile. **Fig. 2. Above right** Marked pes cavus and hammer toes. Note darkened pigmentation. **Fig. 3. Left** Napkin-ring myotonic response elicited by percussion of tongue.



with a population of about three hundred in which, according to the family, "everyone is related." The patient's four grandparents were born in this town and had died at an elderly age. A maternal cousin in young adulthood had received unspecified psychiatric treatment. Members of the father's family were in excellent health. Both the patient and his brother were born in Argentina.

Examination Results. On examination he was muscular appearing, alert, oriented, with a continuous fixed smile (Fig. 1). Blood pressure was normal with no orthostatic change. There was gingival bleeding. Hyperpigmentation of the lower extremities was noted. There were no spider angiomata. Heart and lungs were normal. Abdomen was soft with a palpable spleen three cm below the left costal margin. The stool guaiac test result was positive, but not grossly melanotic. There was pes cavus with hammer toes (Fig. 2). Trousseau's and Chvostek's signs were absent.

Neurologic examination showed normal cognitive functions. There was rhizus sardonicus with drooling and dysarthria. He was easily provoked to laughter. Visual acuity and visual fields, optic disks, and retinae were normal. There was mild anisocoria. There was limitation of voluntary gaze to the left, occasionally upward, and rarely to the right. Optokinetic nystagmus was abnormal with intermittent and slow saccades in all directions. Calorics were normal. There was coarse resting tremor and cogwheel rigidity in all four extremities. Strength was normal, as was muscle bulk. There was intermittent flexion dystonic posturing of the lower extremities, greater on the right than on the left. Percussion myotonia was elicited from thenar eminences, extensor digitorum communis, tongue, and quadriceps (Fig. 3). There was grasp myotonia. Reflexes were hyperactive and symmetrical with a left extensor plantar response. There was blepharospasm, snouting, and hyperactive jaw jerk. Rapid movements were impaired and tremor worsened with action at times. He needed full assistance to stand, and he was unable to take a step. Sensory examination was completely normal.

An evaluation in Argentina disclosed a persistently abnormal prothrombin time and partial thromboplastin times. There was thrombocytopenia. An electromyogram and muscle biopsy were felt to be consistent with myotonia. All other laboratory test results were reported to be normal, including a lumbar puncture.

Laboratory evaluation at The Mount Sinai Hospital disclosed a hemoglobin of 11.4 g/dl, hematocrit 30.7 ml/dl, white blood cell count 8700/μl, prothrombin time 15.2/11.7 sec, partial thromboplastin time 53/42.6 sec, bleeding time greater than 15 sec, fibrinogen 125 mg% (normal 200–400 mg%), and fibrin split products negative at 1:5 and 1:20 dilutions. Factor assay showed Factor V and XI depressed at 39% and 36% respectively. Depression of Factor XI was felt to be congenital, and depression of Factor V to be the result of liver disease. Initial chemistry studies showed slight hyperchloremia with otherwise normal electrolytes, depressed calcium, magnesium, protein, albumin, and normal phosphorus. Creatinine level was persistently 1.3–1.5 mg%, but there was no proteinuria. Results on creatine phosphokinase, liver function tests, erythrocyte sedimentation rate, antinuclear antibody, serum and immunoelectrophoresis, latex fixation, thyroid function tests, blood cultures, and urinalysis were all normal. Plasma iron and iron binding capacity were depressed. Hepatitis B surface antigen and antibody were negative. Serum ammonia level was 77 mcg/dl (normal 15–50 mcg/dl). Serum uric acid was persistently low. A bone marrow examination showed increased eosinophils, immature granulocytes, and magakaryocytes, and normal erythroid prescursors. There were no tumor cells.

A liver spleen scan showed massive splenomegaly and a small liver with diffuse patchy parenchymal uptake that is typical of a cirrhotic pattern. An upper-gastrointestinal study revealed large esophageal varices. A slit-lamp examination showed corneal rings in the upper and lower poles of Descemet's membrane, typical of Kayser-Fleischer rings. A 24-h urine copper was 97 μg (normal 0–37 μg), serum copper 31 μg/ml (normal 65–165 μg/ml). Ceruloplasmin was less than 6.0 mg% (normal 18–57 mg%). On 1000 mg of penicillamine, 24-h urine copper rose to 408 μg, 624 μg and 707 μg on three separate measurements.

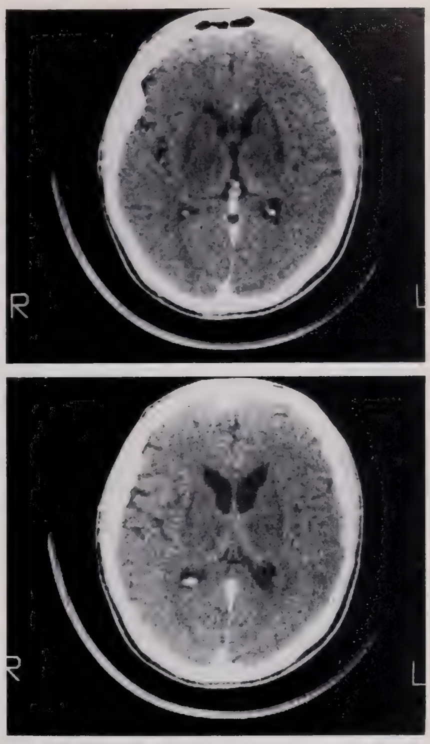


Fig. 4. CT scans showing ventricular enlargement, bilateral slitlike lucencies in putamens, and large bilateral hypodense areas throughout thalami.

An electroencephalogram was normal. A computed tomographic brain scan, with and without contrast, demonstrated bilateral lucent areas in putamens, thalami, and internal capsules, with slit lucent areas laterally in putamens and external capsules (Fig. 4). There was some sulcal and ventricular enlargement. There was no specific enhancement with contrast. An EMG showed bizarre high-frequency discharges and myotonic discharges. Visual evoked potential latencies were normal.

On gastroscopic study stomach and duodenum appeared normal. Esophageal varices were the only source for bleeding. He received three sclerotherapy treatments. While receiving medication he complained of persistent abdominal pain. He had had this pain intermittently for two years and had guarding, although not nausea or vomiting, and had a good appetite. A repeat liver spleen scan showed several wedge-shaped defects consistent with splenic infarcts. The patient's platelet count, white blood cell count, and hemoglobin remained depressed throughout his hospitalization, presumably secondary to splenic sequestration.

The patient's brother had normal CBC, SMA6, SMA12, CPK, prothrombin and partial thromboplastin times, serum copper, 24-h urine copper, and ceruloplasmin (20 mg%). Clinical myotonia was absent, as was pes cavus.

The patient's serum uric acid was persistently borderline to low. A 24-h urine collection for uric acid was normal. A qualitative urine amino-acid electrophoresis was normal. Serum calcium determinations were low, as was albumin. Serum phosphorus was always normal, and a random measurement of ionized calcium was normal.

Discussion

The pattern of abnormalities in this patient is incompatible with a single known pathophysiologic or genetic defect. Portal hypertension, thrombocytopenia, leukopenia, Parkinsonian syndrome with pseudobulbar palsy, pyramidal findings, and dystonia are all explainable on the basis of Wilson's disease, which is confirmed by CT findings and biochemical profile. The history of muscle stiffness on initiation of activity, the preservation of muscular bulk with clinical and electrical myotonia and pes cavus strongly suggest myotonia congenita on clinical grounds. There is no evidence for the pattern of systemic abnormalities seen with dystrophic myotonia. Changes in symptoms with temperature or episodes of paralysis as seen in the presence of paramyotonia or the myotonia of hyperkalemic periodic paralysis were not present in this case. In addition, the history of childhood bleeding suggests that the factor XI deficiency may also be inherited. Thus it appears that there are three genetic diseases present in this individual.

Based on prevalence figures alone for each of these conditions in a mixed population, the coincidence of these genetic disorders would be extremely rare. The figures available from the literature have been gathered in specific populations and may not be entirely applicable in calculating the likelihood of all three of these disease entities occurring together. For example, the prevalence of factor XI deficiency is estimated in a population of Ashkenazi Jews (8, 9) and the prevalence of 42 per million for recessive myotonia congenita is estimated by Becker (10) in a German population.

Estimates of prevalence for Wilson's disease have been revised over the years and has been reviewed most recently by Scheinberg and Sternlieb (11). Their best estimate is approximately 30 per million, based upon an average of regional world prevalences.

Considering only myotonia congenita and Wilson's disease, this yields a combined probability of the two diseases occurring in the same patient, assuming they are independent, as 1 to 2 in one billion. This estimate assumes independent genetic transmission of the two diseases in the family. The alternative is to postulate that one or the other entity is a new mutation in this patient. More detailed information concerning the family is not available to assess this adequately, except for the brother, whose normal urinary copper excretion but low normal ceruloplasmin level argues for his being heterozygous for the WD gene (11, 12). Thus the gene for Wilson's disease is present in the family. It is well documented that family members of Wilson's disease patients may harbor the defect without clinical expression, and families exist in which infant siblings of patients may have died of undiagnosed Wilson's disease. Therefore, the lack of a symptomatic family history of Wilson's disease is not adequate to invoke a new mutation as an explanation for its singular appearance in this patient.

Becker's data (10, 13) show that myotonia congenita may be inherited as an autosomal recessive disorder. The documentation of sporadic cases of myotonia congenita has been reviewed in the historical literature by Kuhn (13), including cases seen by Leyden, Bernhardt, Erb, Thomasen, and Klein, in which the phenomenon of the sporadic case of myotonia congenita appears all too commonly for autosomal dominant inheritance to be the sole pattern of inheritance, as was believed earlier in this century. Consequently, the presence of myotonia without a family history in this case also does not necessitate invoking a new mutation as an explanation of this patient's singularity in this family.

If in addition to the above considerations we add the possible factor of consanguinity in this family, the probability of finding rare diseases concurrently is higher. The family originated in a small village in Spain, a country with a high consanguinity rate (14). Of interest, family studies of both Wilson's disease and recessive myotonia congenita have noted high consanguinity (Bearn [15], Ionasescu [16], and Becker [10]).

The alternative to conceptualizing this case as a chance occurrence of three genetic diseases is to attempt to delineate a pathophysiologic connection, which becomes purely speculative in this instance. Rapaport (17) and Naeye (18) showed that factor XI deficiency may result from cirrhosis, which was also seen in this patient, thus linking the hematologic disorder to Wilson's disease. The myotonia in the setting of Wilson's disease is more difficult to unify because present theoretical conceptions of the defects in these diseases are quite unrelated. Myotonia is thought to result from a decrease in muscle membrane chloride conductance (13, 19, 20–22). No studies have been done on ions like copper in relationship to the investigated biophysical alteration proposed for myotonia. In Wilson's disease, the basic molecular pathology is not known. Present speculation centers on unifying the fact that biliary copper excretion and copper destined for ceruloplasmin are separate pools in the hepatocyte, and both pathways are disordered (Epstein [23], Walshe [31] and Scheinberg and Sternlieb [11]). Membrane effects of copper accumulation have been studied (11, 12, 24, 25), although with respect to sodium-potassium ATPase and not chloride conductance.

Copper has been seen to accumulate in muscle in a patient with Wilson's disease (26), an intriguing observation with respect to our patient, but of no clinical significance in the reported one. Even if we were to hint at some pathophysiologic mechanism linking the two diseases in this case, the absence of myotonic phenomena in the voluminous numbers of case reports of Wilson's disease in the literature suggest that they are not associated metabolic defects.

The computed tomographic appearance in our patient seems typical of those presented in the literature by Walshe (27), Kendall (28), and Hamik (29) in showing bilateral lucencies in the thalami and basal ganglia with slitlike lucencies in the putamens. Cerebral atrophy and moderate ventricular enlargement, noted in our case, were the most frequently found CT abnormalities in Walshe's series. In Kendall's small series of patients, hypodense areas in the basal ganglia on CT correlated with the severity of the extrapyramidal disorder.

Several clinical features in this case deserve highlighting. Pes cavus undoubtedly represents a manifestation of recessive myotonia congenita. Becker (10) observed that this finding was characteristic of the recessive form of myotonia congenita; it is generally not found in dominant myotonia congenita. The hammer toes and equinovarus posture probably resulted from dystonia. Our patient's skin was pigmented, especially in the lower extremities. This may be an expression of Wilson's disease as described by Strickland and Leu (30) and may be related to copper stimulating melanin production. Gingival bleeding and easy bruising were present in half of 40 patients with Wilson's disease reviewed by the same authors (30), suggesting that these early symptoms in our patient may indeed have been due to Wilson's disease rather than to congenital factor deficiency. We did not find symptomatic hypocalcemia, which has been seen in other patients with Wilson's disease (7). Our patient's first manifestation was depression and personality change, a clinical feature emphasized in the initial literature and subsequently by Scheinberg and Sternlieb (11). The brain lesion responsible for producing psychiatric disturbance is elusive and perhaps awaits more functional definition of the interaction of copper with neuronal metabolism in nonnigral dopamine systems.

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Histopathology of the Breasts of 12 Women Receiving Long-Term Exogenous Androgen Therapy

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Abstract

The effects of long-term androgen administration on the histology of the human breast were assessed in 12 female-to-male transsexuals. Studies included the evaluation of lobules and intralobular and extralobular fibrous stroma of breasts of women treated with androgens for an average duration of 13.8 months. Results demonstrated the variability of stromal connective tissue and epithelial changes in these patients. Seven of the twelve patients (53.8%) demonstrated moderate to severe lobular atrophy or intralobular fibrosis or both. The data do not disclose the causes of the variability.

The clinical effects of prolonged androgen administration in mature premenopausal women and the subsequent histological changes induced in the breast have not been documented in the literature. We found only a single case, reported by Merkel and Gross (1), who describe the histologic effects on the breast after 4 years of testosterone administration to a 31-year-old woman. The authors found atrophy with loss of mammary lobules and periductal elastosis. Our study includes 12 female-to-male transsexual individuals who had variable periods of androgen therapy prior to mastectomy. The uncommon nature of these observations of human breast tissue in 12 female-to-male transsexual patients during long-term androgen therapy prompted this report.

Materials and Methods

Twelve female-to-male transsexuals were studied between 1982 and 1986. Their ages ranged from 20 to 42 years, with a mean age of 30.2 years. The androgen employed by referring physicians was testosterone enanthate or testosterone cypionate, 400 mg intramuscularly every 3–4 weeks. Pretreatment clinical features, such as regularity of menstrual function and presence or absence of hirsutism, acne, or obesity, were noted. A Ponderal Index (Pondex) was employed (2) which measures the height divided by the cube root of the weight (a Pondex less than 12 is considered obese). Prior to androgen treatment laboratory studies were obtained of plasma testosterone (T), LH, FSH, dehydroepiandrosterone sulfate (DHAS), and prolactin (PRL), which were determined by radioimmunoassay. The technique of the radioimmunoassays was reported previously (3). In most instances pretreatment blood values were determined on more than one occasion. Specimens were obtained during the follicular phase of the menstrual cycle. In three subjects a pelvic ultrasound examination was performed prior to androgen treatment.

Psychiatric evaluation and clearance were obtained on all patients prior to treatment with testosterone enanthate and prior to bilateral mastectomy. The latter procedure is considered necessary in the treatment of sex gender reassignment by the Gender Dysphoria Association of Stanford, California. Eight of the twelve patients subsequently had bilateral salpingooophorec-

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TABLE 1

Clinical and Laboratory Data, 12 Female-to-Male Transsexuals Prior to Androgen Treatment

PT no.	OR age	R × T (mo.)	Menses	Hirsutism	Pondex	T*	LH/FSH†	DHAS‡	PRL§
1	42	14	Reg.	0	12.5	870	2.82		31
2	24	2	Reg.	1+	11.2	890	1.81	6.03	33
3	37	13	Reg.	1+	12.4	400	1.11	2.11	63
4	23	23	Reg.	0	12.3	580			18
5	26	35	Reg.	1+	11.6	1,070	1.87	2.68	14
6	27	29	Oligo.	0	13.5	750	3.60		17
7	20	11	Reg.	0	13.3	690	2.9	1.80	12
8	21	6	Reg.	1+	12.9	800	1.33	4.30	11
9	40	10	Reg.	0	13.3				
10	34	9	Reg.	0	12.0	450	1.63	0.84	12
11	29	10	Reg.	0	12.9				
12	39	3	Reg.	1+	11.9	580	0.9	0.93	13
n	12	12			12	10	9	7	10
Mean	30.2	13.8			12.5	708	2.0	2.7	22.4
SD	7.5	9.8			0.7	199	0.9	1.7	15.5

* Range in normal women, 250–800 pg/ml; 0.86–2.75 nmol/liter.

† Normally <2.5 in adult women except during ovulatory surge.

‡ Range in normal women, 0.76–3.4 μg/ml; 2.0–8.7 μmol/liter.

§ Range in normal women, 5–25 μg/liter.

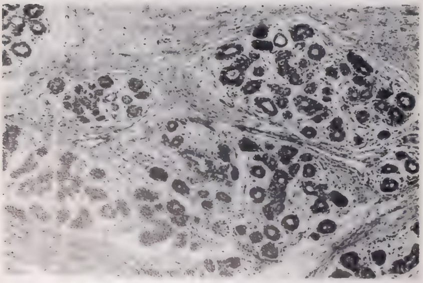
TABLE 2

Histologic Features of Breast Tissue following Androgen Therapy to 12 Female-to-Male Transsexuals

PT no.	Lobules	Introlobular fibrous stroma	Extralobular fibrous stroma
1	Rare	Increased	Increased
2	Absent	—	Increased
3	Normal	Normal	Normal
4	Few, small	Normal	Normal
5	Normal	Normal	Normal
6	Absent	—	Increased
7	Few	Increased	Increased
8	Normal	Increased (focal)	Normal
9	Normal	Sl. increase	Normal
10	Normal	Sl. increase	Normal
11	Few	Increased	Increased
12	Normal	Increased	Increased

tomy and hysterectomy. One 35-year-old, untreated female who had a mastectomy for carcinoma of the breast was used as a control subject to compare the histopathological findings of the remaining normal breast tissue to findings of our series of 12 androgen-treated women.

The breast tissue samples from the mastectomy specimens consisted of one or more sections per breast (two to eight per patient) stained by the hematoxylin-eosin (H&E) method. Observations were made blindly by the reviewing pathologist (ISS) who had no knowledge of each individual patient's age, parity, or dose or duration of androgen administered. The evaluation consisted primarily of recording the presence and relative



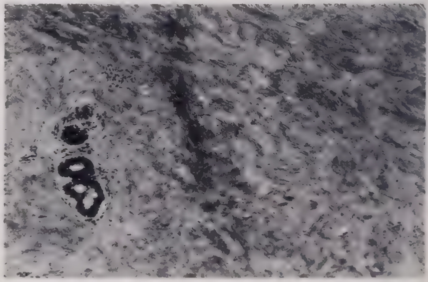


Fig. 1. Left: Control subject, 35-year-old woman. Several lobules with loosely arranged intralobular stroma (hematoxylin & eosin stain, original magnification ×100).

Fig. 2. Right: Absence of lobules. rare mammary ducts within a dense collagenous, fibrous extralobular stroma (patient 2). Dense collagen imparts smudgelike appearance to stroma. (hematoxylin & eosin stain, original magnification ×100).

frequency of mammary lobules and the amount of intralobular fibrous stroma as measures of lobular atrophy. The general (extralobular) stroma was assessed as either normal or increased in collagen content, based on the H&E stain. Special stains to evaluate elastic tissue were not available to the reviewer.

Results

In the 12 patients, the mean duration of testosterone treatment (Table 1) was 13.8 + 9.8 months. Only one subject had oligomenorrhea, but mild hirsutism was noted in five patients. Three patients had moderate acne prior to treatment. No clitoromegaly was observed in any patient. Plasma testosterone was elevated in three patients (range 870–1,070 pg/ml, or 2.99 nmol/L) and the LH/FSH ratio was increased >2.5 in two of nine subjects tested. Two of seven subjects had an elevated plasma DHAS value, and three patients were hyperprolactinemic (range 31–63 μg/liter) with no detectable galactorrhea (Table 1). Two of 12 subjects (patients 3 and 10) studied with pelvic ultrasonography had sonographic evidence of multifollicular ovaries with normal plasma testosterone values (Table 1).

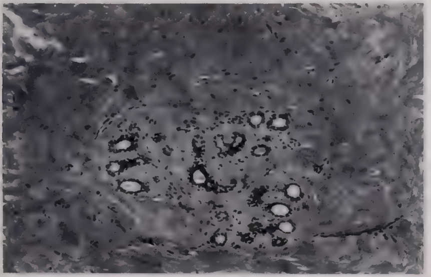
For the histologic findings in the sampled mastectomy specimens (Table 2), parenchymal involution was assessed primarily by the status of the mammary lobules as characterized by their frequency in several miscroscopic fields and the presence and degree of intralobular fibrosis. The presence of general stromal fibrosis was also noted (4). None of the samples showed atypical epithelial hyperplasia or features characteristic of gynecomastia. Breast parenchyma from the control subject exhibited plentiful lobules showing the normal loosely arranged intralobular connective tissue with a more compact extralobular collagenous stroma (Fig. 1).

Severe lobular atrophy was found in three patients (patients 1, 2, and 6) (Figs. 2, 3). Two of these had been on androgen therapy for 14 and 29 months, respectively, and one had received androgen for only two months. Specimens of four additional patients (patients 4, 7, 11, and 12) showed moderate lobular atrophy, as indicated by a diminished number of lobules and/or intralobular fibrosis (Fig. 4). The remaining five patients (patients 3, 5, 8, 9, and 10) who were receiving androgen therapy prior to mastectomy for a period ranging from 6 to 35 months had normal to mildly atrophic changes in their breasts. A variety of histologic findings are described in breasts of women on long-term androgen therapy (Figs. 2–4).

Discussion

The effects of androgens on human females in their reproductive years are difficult to study, because the indications for their use are limited and the virilizing effects are usually unacceptable. Recently, histopathologic studies of female-to-male transsexuals have clarified the effects of androgens on the ovary (3, 5) and uterus (3). An opportunity was presented for us to study the histopathology of the breasts of 12 female-to-male transsexuals who had bilateral mastectomy performed following a variable duration of treatment with testosterone. Although approximately 25% of such subjects exhibited polycystic ovarian disease clinically prior to androgen therapy (6), most have had regular ovulatory menses.

A series of autopsied women between the ages of 15 and 56 years who died unexpectedly were studied by Longacre and Bartow (7). This



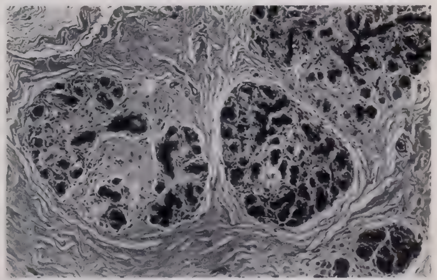


Fig. 3. Left One of the few lobules found shows intralobular fibrosis in a dense extralobular stroma (patient 1) (hematoxylin & eosin stain, original magnification ×100).

Fig. 4. Right Increased intra- and extralobular fibrous stroma (patient 12) (hematoxylin & eosin stain, original magnification ×100).

afforded the opportunity to correlate breast morphology with dated endometrial tissue in endocrinologically normal women. The authors demonstrated marked cyclic variations in the histology of the breast during the menstrual cycle in the 75 premenopausal women studied. Also studied were 12 postmenopausal women in whom the lobular epithelial elements were markedly decreased and the intralobular collagen was dense and hyalinized. Acinar lumina were small and decreased in number. The amount of periductal elastic tissue was increased.

The variability of stromal connective tissue and epithelial changes in our patients following androgen administration may be related to the interconversion of androgens to estrogens peripherally. This may affect the morphology of the breast, resulting in findings similar to those seen in the early proliferative phase of the menstrual cycle (7).

Although we were unable to demonstrate a direct correlation between length of androgen administration and the degree of mammary parenchymal atrophy, it appears that exogenous androgens exert an effect that simulates the morphologic changes observed in postmenopausal women.

Acknowledgments

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Pure Gonadal Dysgenesis and Gonadal Tumors: Report of Three Cases and Review of Literature

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Abstract

The clinical and pathologic features in three patients with pure gonadal dysgenesis and 46 XY karyotype are presented. Two of them had associated germ-cell tumors, consisting of bilateral gonadoblastoma and dysgerminoma that was bilateral in one patient and unilateral in the other, and multiple calcifications. One patient—the oldest, whose condition was diagnosed more than 14 years prior to surgery—had streak gonads with multiple calcifications. The histogenesis and natural history of these rare conditions are discussed, including the potential for neoplasia in the dysgenetic gonad and the possible "burning out" by hyalinization and calcification of associated germ-cell neoplasias. The validity of early surgical gonadectomy, even in the absence of a gonadal tumor, is discussed in relation to these patients, in whom diagnosis was early but gonadectomy was delayed.

Pure gonadal XY dysgenesis was first described in 1955 by Swyer as an intersex disorder. The association of gonadal dysgenesis with gonadal neoplasms, estimated as 25%, is considered to occur almost exclusively in the presence of a Y chromosome. The most prevalent neoplasias are gonadoblastoma and dysgerminoma; their development may represent an abnormal tissue response to a genetic anomaly.

Three patients with pure gonadal dysgenesis diagnosed early are reported on here. Two had associated gonadal tumors, and one had streak gonads with calcifications. Morphologic description and discussion of the histogenesis of these uncommon gonadal anomalies may be helpful in developing an insight into their natural history and for the management of patients with these disorders.

Case Histories and Pathology

Case 1. A 16-year-old phenotypical female with primary amenorrhea had experienced a growth spurt from age 8 to 12; breast bud and axillary and pubic hair developed at age 13. Vaginal smear demonstrated insufficient estrogen production, and buccal smear demonstrated no Barr bodies. Peripheral lymphocytes were 46 XY. No mosaicism was found. She had undergone tonsillectomy and adenoidectomy at age 5. The family history was not contributory.

On examination, the patient was a white female, 5′11″, weighing 160 lb. Blood pressure was 128/90 mm Hg. The facies was notable for moderate acne. She had minimal breast development. There were no abdominal or inguinal masses. There was normal female axillary and pubic hair development. Introitus was normal; the vagina ended in a small cervix and the uterus and adnexae were not palpable. Preoperative intravenous pyelography was normal. At laparotomy, the patient was found to have an infantile uterus, normal fallopian tubes, a streak left gonad, and a

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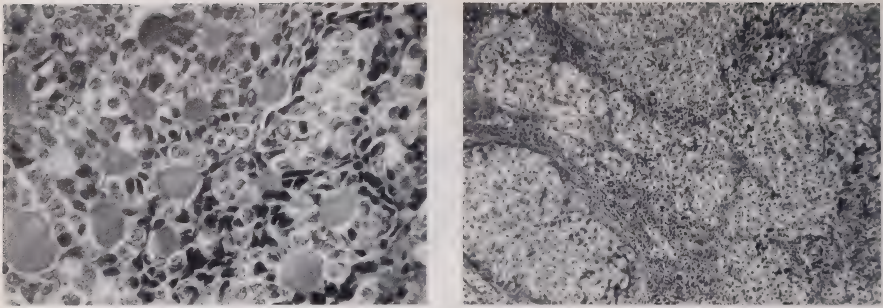

Fig. 1. Case 1. Left Gonadoblastoma, showing eosinophilic globular masses, primitive germ cells surrounded by undifferentiated sex-cord cells (H&E ×40 original magnification). **Right** Dysgerminoma in gonadoblastoma: predominance of primitive germ cells adjacent to lymphoid cell infiltrates (H&E ×25 original magnification).

right gonad having the gross appearance of testicular tissue. Bilateral gonadectomy was performed.

Pathologic examination revealed the presence of gonadoblastoma and areas of dysgerminoma in both gonads. No normal germ cells were found in either gonad, which were composed, in their nontumoral constituents, of fibroconnective tissue and islands of interstitial cells, similar to Leydig cells. No testicular tissue was found in either gonad. The tumor showed the characteristics of gonadoblastoma: eosinophilic globular masses of basement membrane material and primitive germ cells, surrounded by immature, undifferentiated sex cord cells (Fig. 1). In some areas there was a predominance of primitive germ cells lying in sheets with no particular arrangement, adjacent to lymphoid cell infiltrates (Fig. 1). This was the dysgerminomatous component which predominated in the right gonad, accounting for its being larger than the left. Also seen were multiple calcifications, both in the nontumoral areas of the dysgenetic gonad and in the gonadoblastoma, confluent with the hyaline bodies.

Case 2. A 20-year-old woman with primary amenorrhea was first seen at age 16. She had a normal growth spurt, with breast and pubic and axillary hair development. Peripheral lymphocytes were 46 XY with normal G banding, and vaginal smear for estrogenization demonstrated atrophy. Ultrasound of the pelvis demonstrated a uterus measuring 4 × 2 × 2 cm. The right gonad was 2 × 1.5 × 1.2 cm, and the left gonad was 1.8 × 1.6 × 1 cm. Skull x-rays demonstrated no pathologic intracranial calcifications, noncalcified pineal, and unremarkable pituitary fossa and petrous pyramids. When the patient was reevaluated at age 20, by another physician, she again underwent peripheral lymphocytic karyotyping, which was 46 XY. Pelvic ultrasound findings were unchanged. Serum testosterone was 0.35 ng/ml (normal female range for that laboratory). FSH was 97.5 mIU/ml.

On physical examination, the patient was a very tall white female. Height was 5′11″, weight 142 lb, blood pressure 100/60 mm Hg, pulse 80. Breasts were Tanner stage 4. The abdomen was without masses or hernias. The vagina was small, and there was normal female escutcheon. The cervix was hypoplastic, and the uterus was small and adnexae nonpalpable. Extremities were long, with large hands and feet.

The patient had laparotomy and bilateral gonadectomy. At that time, she was found to have a very small uterus, normal round ligaments, and hypoplastic fallopian tubes bilaterally. The right gonad was in streak form, displaced laterally to the lateral pelvic wall near the iliac vessels. The left gonad was larger, contained a cyst 0.5 cm in diameter, had multiple vascular markings on the surface, and was also located on the left pelvic sidewall. The left gonad was karyotyped 46 XY.

Pathologic examination revealed the presence, in both gonads, of nests of germ cells and primitive sex-cord cells, surrounding both germ cells and hyaline globules. The left gonad showed an area of pure germ-cell proliferation that constituted a small dysgerminoma (Fig. 2). The cystic lesion adjacent to the fallopian tube was of mesonephric origin. Multiple microscopic calcifications were found throughout the dysgenetic gonad, in which no normal germ cells were seen. No testicular tissue was found in either gonad, and the tissue not involved by gonadoblastoma was that of streak gonads.

Case 3. A 38-year-old gravida 0 woman with a history of primary amenorrhea had experienced

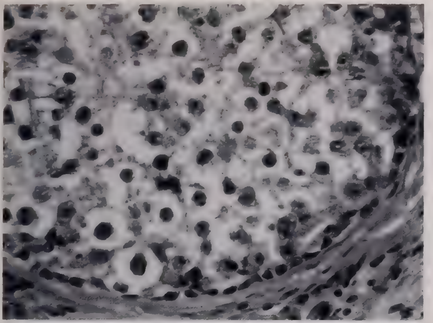

Fig. 2. **Case 2.** Dysgerminoma in gonadoblastoma, showing predominantly primitive germ cells (H&E ×160 original magnification).

a normal growth spurt in early adolescence, but no spontaneous breast development. She reported scanty axillary and pubic hair growth until the age of 24, when she was given oral estrogen and progestin therapy, with subsequent pubic and axillary hair development, plus withdrawal bleeding and breast development. She underwent exploratory laparoscopy at that time, revealing "no ovaries" and presumably the presence of uterus and fallopian tubes. At age 33, she underwent repeat laparoscopy and "ovarian" biopsy showing "hilar cell hyperplasia." Peripheral leukocytes were 46 XY and the diagnosis of gonadal dysgenesis was made. She had multiple medical illnesses, including type I diabetes mellitus, varicose veins, and morbid obesity. Prior surgeries included appendectomy, tonsillectomy in childhood, plus varicose vein stripping at age 19.

Significant family history included a great-aunt with primary amenorrhea. The patient was taller than other family members, most of them coming to her shoulders. Physical examination revealed a tall, obese, caucasian woman, height 5′9-3/4″, weight 285 lb. Blood pressure was 140/100 mm Hg, pulse 80. Breasts were Tanner stage 3. Abdominal examination was negative for any masses or hernias. The vagina was small, with a small cervix. The uterus was nonpalpable. No adnexae were palpated. Extremities were long, with large hands and feet. Laboratory values obtained preoperatively included serum estradiol of 28 pg/ml, LH 29.8 mIU/ml, FSH 57.8 mIU/ml, dehydroepiandrostenedione sulfate 42.7 ng/L, testosterone 108 ng/dl, prolactin 19.6 ng/ml, cortisol 28 μg/dl, 17-hydroxyprogesterone 0.58 ng/L, Δ^4-androstenedione 205 ng/dl, thyroxine 8.8 ng/dl, thyroid-binding globulin 21 ng/ml.

The patient subsequently underwent exploratory laparotomy with gonadectomy. At the time of surgery, she was noted to have an infantile uterus and fallopian tubes. The left fallopian tube contained no fimbriae. In the midaspect of the right fallopian tube a tense, 3-mm cyst was found; otherwise the tube appeared grossly normal. The gonads appeared to be streaks bilaterally.

Pathologic examination of the gonads revealed a fibroblastic stroma embedded in dense collagen fibers, somewhat reminiscent of ovarian stroma, with numerous calcifications of various sizes, varying from microscopic foci to grossly recognizable small, hard, whitish areas (Fig. 3). No germ cells, however, were identified. Large clusters of ovoid cells with round nuclei and prominent nucleoli, surrounded by a finely granular cytoplasm, similar to both ovarian hilar cells and testicular interstitial cells (Fig. 3), were found. Also seen were mesonephric remnants, bilaterally.

Follow-up. All three patients were given substitutive hormone therapy. Patient 1 devel-

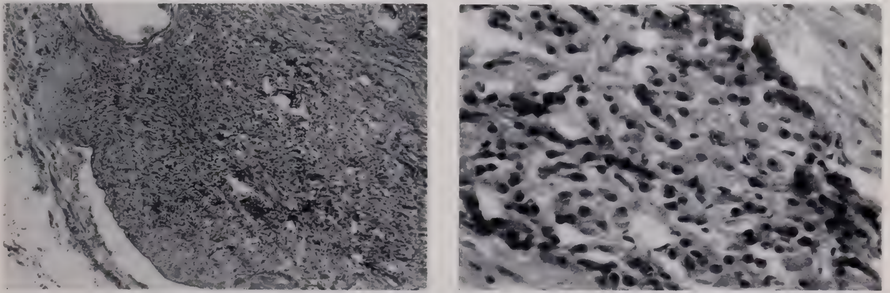

Fig. 3. **Case 3.** **Left** Gonad with fibroblastic stroma, calcification (left top), and interstitial cells (H&E ×25 original magnification). **Right** Cluster of interstitial cells, similar to ovarian, hilar, and Leydig cells (H&E ×100 original magnification).

oped severe endometrial adenomatous hyperplasia, diagnosed on dilatation and curettage for vaginal bleeding after 6 years of estrogen therapy and 1 year of estrogen and progesterone therapy, and underwent hysterectomy. No residual tumor was found. The other patients did not develop any subsequent neoplasia and are well 3 years (patient 2) and 2 years (patient 3) after gonadectomy.

Discussion

All three patients had pure gonadal dysgenesis and a 46 XY karyotype; two had associated gonadal tumors.

Gonadal dysgenesis is commonly seen in Turner's syndrome with an associated 45 X karyotype. Pure gonadal dysgenesis is less frequent; it occurs in phenotypic females with gonadal dysgenesis, primary amenorrhea, hypoestrinism, poorly developed secondary sexual characteristics with generally elevated gonadotropins, and absence of Turner's syndrome (1). Hirsutism and virilization are occasionally seen, but only at or after puberty. Karyotyping reveals a 46 XY in the majority of patients (1). The three reported patients were all phenotypic females, with histologically proven bilateral streak gonads, presenting with amenorrhea, poorly developed secondary sexual characteristics, and absence of Turner's syndrome. None was virilized but all three had 46 XY karyotype with no mosaicism. In case 1, the gross appearance of the gonads suggested mixed gonadal dysgenesis because of the asymmetric gonads and the testislike appearance of the right gonad which, along with chromosomal mosaicism, characterizes mixed gonadal dysgenesis. Histologically, however, no testicular tissue was found.

Natural History of Gonadoblastoma. The presence of a Y chromosome with the concomitant H-Y antigen is responsible for the organization of a male reproductive system and, ultimately, for spermatogenesis (2). Its absence, in the indifferent gonad, leads to the development of an ovary (3). XY germ cells cannot survive without testicular organization (4) and will disintegrate, leaving streak gonads. It also seems that the presence of 20% Sertoli cells in gonadal mass is critical to the development of a normal testis (4, 5). The failure of this development may be due to genetic factors, such as a defective male antigen controlling gene (MACG) located on the short area of the X chromosome (6), or to an autosomal anomaly, such as an abnormality of a structural gene coding for the protein sequence of the H-Y antigen (7). The nature of this failure is still poorly understood, but its timing became more evident with knowledge of early gonadogenesis. If the failure in the testicular organogenesis occurs before the secretion of its first hormone, the müllerian inhibitory factor (MIF), the internal genital organs will develop in the female direction, under the influence of the maternal sex hormones, and the phenotype, at birth, will be female (5). This was the case in the three patients reported on here. After puberty, however, a normal gonad being absent, these patients became symptomatic and presented to the physician with amenorrhea, abnormal growth spurt, and insufficient sexual development.

The diagnosis, by cytogenetics, of a 46 XY karyotype in a phenotypical female should be followed by gonadectomy as soon as possible, because of the risk of neoplastic transformation of the dysgenetic gonads (1). However, in two of the three patients discussed here, gonadectomy was performed years after puberty, in one 14 years after the diagnosis. Bilateral gonadoblastomas were found in the two younger patients, associated with dysgerminoma, unilateral in one case and bilateral in the other. The older patient had streak gonads with no visible gonadal-cell tumor and extensive calcifications.

Gonadoblastoma is a rare gonadal tumor, first described by Scully in 1953. Over 100 cases have been reported. In a review of the world literature on neoplasms in dysgenetic gonads from 1953 to 1983, Troche and Hernandez (1) report a 90.7% association with a Y chromosome in the 119 patients who had chromosome analysis performed. The majority of associated neoplasms, 103 (53%), were gonadoblastomas, with 38 (19.6%) additional dysgerminomas.

Gonadoblastoma is almost exclusively found in patients with abnormal chromosomes and dysgenetic gonads and accounts for two-thirds of all gonadal tumors in phenotypical females with abnormal gonadal development (8).

Histologically, gonadoblastoma is composed of immature germ cells, surrounded by undifferentiated sex-cord cells, reminiscent of granulosa or, even more, of Sertoli cells; it is therefore a mixed germ-cell–sex-cord tumor. Since a variety of germ-cell developmental anomalies have been described, culminating with gonadoblastoma, and no cases of metastatic gonadoblastoma have been reported (9), this lesion may be considered intermediate between abnormal gonadal development and a true neoplasm. Its common association with dysgerminoma and less common association with other malignant germ-cell tumors (embryonal carcinoma, yolk-sac tumors, choriocarcinoma) should, however, prevent a false sense of security, because, even if considered a "tumor in situ," gonadoblastoma entails a high risk for subsequent development of malignant, and occasionally fatal, germ-cell tumors (9–11).

The natural history of the dysgenetic gonads and their associated tumors is poorly understood. It seems highly probable that the same gene that codes for the H-Y antigen is also responsible for the neoplastic changes in the dysgenetic gonad (1). Histologically, a disorderly attempt to form a testis in a genetically abnormal individual may result in a pattern of immature germ cells admixed with immature sex-cord cells, the latter producing a basement membrane material forming hyaline "globules" similar to Call-Exner bodies (12). These features are reminiscent of gonadoblastoma.

Hyalinization and Calcifications. Of particular interest in the natural history of gonadoblastoma is the process of hyalinization and the calcifications, present in 50% of all cases and detected by pelvic x-ray examination—sometimes an initial symptom of a gonadal anomaly (13). These calcific masses, seen in all three presented cases, may result from extensive hyalinization of tumor nests. Hyalinization and calcification represent a regression of the tumor, and gonadoblastoma presents the greatest potential for retrogressive changes of any gonadal tumor, being subject to fibrosis and calcification of such magnitude as to obliterate its original structure (12). In case 3, the absence of gonadoblastoma and presence of extensive calcifications may represent the "burning out" of a dysgenetic neoplastic process. The presence of numerous nests of Leydig-type cells in this case may represent an independent process, which takes place usually after puberty, influenced by gonadotropins. The interstitial cells persist when all the other components (germ cells, sex-cord cells) have disappeared, and it has been demonstrated that they respond to human chorionic gonadotropin stimulation and secrete androgenic steroids (12).

The three patients reported on here illustrate possible histogenetic patterns in pure gonadal dysgenesis and gonadoblastoma: development of dysgerminoma, in the two younger patients, and possible "burning out" of the tumor, in the older patient, with preservation of interstitial Leydig cells.

Importance of Prompt Gonadectomy that Preserves the Uterus. The indication for prompt gonadectomy after diagnosis of gonadal dysgenesis associated with an XY karyotype remains valid even in the absence of a gonadal tumor, given the high risk for tumor development and the biologically malfunctioning gonads. However, preservation of the uterus is important in view of the new reproductive technologies, which include embryo transfer and oocyte donation. Individuals with pure XY gonadal dysgenesis could theoretically experience biologic motherhood.

The review of the histogenesis and natural history of two very rare conditions, pure gonadal dysgenesis and gonadoblastoma, and their surgical and hormonal therapeutic implications may offer some additional insight into these rare pathologic entities.

Acknowledgments

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Fatal Cerebrovascular Thrombosis in a Young Woman:

An Unusual Complication Associated with Hypochromic Anemia and Thrombocytosis following Surgery

DEBRA S. HELLER, M.D., NAFEES K. PERVEZ, M.D., AND JEROME KLEINERMAN, M.D.

Abstract

A 26-year-old woman with mild thrombocytosis had a fatal cerebrovascular accident four days after a myomectomy and ovarian cystectomy. At autopsy thrombi were noted in branches of both pulmonary arteries, the right renal and left dorsalis pedis arteries, as well as massive infarction of the left cerebral hemisphere and right kidney. Smaller infarctions were present in the lungs and spleen. This case is reported as an unusual cause of postoperative diffuse, intravascular thrombosis in a young female with mild thrombocytosis.

Cerebrovascular accidents are rare in healthy young individuals and most commonly are associated with ruptured berry aneurysms (1). Iron-deficiency anemia and thrombocytosis have been reported as laboratory manifestations associated with thrombotic complications and cerebrovascular accident in young as well as elderly patients (2, 3). These patients have platelet counts of a million or more and are considered at increased risk for development of thrombotic and hemorrhagic complications (2–4).

We observed a similar case in a 26-year-old woman with mild preoperative thrombocytosis of 786,000 who developed a fatal cerebrovascular accident and diffuse intravascular thrombosis four days following myomectomy and ovarian cystectomy. This case is reported to emphasize the ominous import of even mild thrombocytosis in patients undergoing elective surgery, and to record this unusual cause of cerebrovascular thrombosis in an otherwise healthy young woman.

Case Report

A 26-year-old white woman was admitted to the hospital for myomectomy and resection of a right adnexal mass. She consulted her physician 3 weeks prior to admission with a three-month history of pelvic pain. Pelvic ultrasound revealed a leiomyomatous uterus and a 6.0 × 3.5 × 3.0 cm solid right-adnexal mass. Ferrous sulfate therapy for anemia (200 mg three times daily) and norethindrone acetate therapy to stop menstrual bleeding (5 mg/day) was started. Her history was negative. Preoperative laboratory determinations were white-blood-cell count 7,900/cm^2, red-blood-cell count, 3,920,000/cm^2, hemoglobin 9.8 g/dl, hematocrit 30.4%, mean corpuscular volume 77.6, mean corpuscular hemoglobin 25.0, mean corpuscular hemoglobin concentration 32.3, platelets 786,000/cm^2.

The patient underwent multiple myomectomies and resection of a right ovarian cyst showing endometriosis. Postoperatively, she was continued on the same dose of ferrous sulfate and norethindrone acetate. Her initial postoperative course was unremarkable, but on the fourth post-

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operative day, she was found in bed mute but conscious, with right hemiplegia. Laboratory values at this time were white-blood-cell count 10,900/cm^2, hemoglobin 9.2 g/dl, platelets 850,000, and normal blood gases and chemistries.

She was transferred to The Mount Sinai Medical Center, where a computerized-tomography scan of the brain revealed slight compression of the frontal horns of the left ventricle and nonvisualization of the left middle cerebral artery. The patient developed a fever of 101.6°F on postoperative day 5 and became more lethargic. The paralysis persisted. Lumbar puncture showed an opening pressure of 360 mm, with protein 27, glucose 89, white blood cells 1, red blood cells 430. The patient developed a dilated reactive left pupil and left third cranial nerve palsy 55 min later, which resolved with mannitol and dexamethasone. The patient was intubated prophylactically and sent to the intensive-care unit. Repeat computerized-tomography scan of the brain showed a low-attenuation lesion of the left hemisphere with compression of the left lateral ventricle and shift of the third ventricle to the right of the midline.

On the sixth postoperative day the patient became comatose with papilledema, and fixed dilated pupils developed over the course of the day. Over the next 8 days, multiple coagulation studies were performed, all with similar results. On postoperative day 13, prothrombin time was 16.9 sec/12.5 sec, partial thromboplastin time 36.1 sec/29.7 sec, fibrinogen 515 mg/dl, and fibrin split products were less than 10 μg/ml. Diabetes insipidus, hyperglycemia, and fluctuation in blood pressure and temperature developed. On postoperative day 10 electroencephalography showed no brain activity. Repeat electroencephalography on postoperative day 13 confirmed this finding, and the patient was pronounced dead.

At autopsy, thrombi were found in the lower lobar branches of both pulmonary arteries, the right renal and left dorsalis pedis arteries, and antecubital veins bilaterally. Microemboli were seen in small portal and myometrial vessels. The right kidney was massively infarcted, and smaller infarcts were present in the lower lobes of both lungs and in the spleen. The left cerebral hemisphere was massively infarcted. Microscopically, all infarcts were compatible with an age of 3–5 days. Evaluation of potential transplant donors has revealed viable organs after brain death (5), so the visceral infarctions probably occurred 3–5 days prior to death. The cerebral infarct antedated the visceral infarcts correlating with the onset of coma. Histopathologic changes in the cerebral infarct were consistent with no progression of pathologic changes after the development of brain death (6), occurring on or about the sixth postoperative day.

The cardiac valves were without vegetations, and there were no septal defects. The spleen showed myeloid metaplasia with immature myeloid cells and megakaryocytes. The marrow was hypercellular with increased megakaryocytes as well as erythroid and myeloid precursors. There was no stainable iron in the marrow and minimally increased reticulin. Review of the preoperative peripheral smear showed increased platelets and hypochromic, microcytic red cells.

Discussion

The case reported here demonstrates the occurrence, in a young postoperative woman, of thrombotic complications in association with low-level thrombocytosis, with fatal consequences. No source (endocardial vegetations, septal defects in the heart, or venous thrombi in the lower extremities) was identified to account for the thrombotic complications in the systemic and pulmonary circulations. An interesting finding at autopsy was the presence of myeloid metaplasia in the spleen in association with a bone marrow that was neither depleted nor replaced. The iron deficiency anemia in this patient was not severe; hence, the finding of myeloid metaplasia in the spleen is consistent with and suggestive of an incipient myeloproliferative disorder. Incipient myeloproliferative disorders may be present with minimal or no clinical evidence (7).

The elevation of platelets (786,000/cm^2) in this patient was initially felt to be secondary to iron deficiency anemia. This type of thrombocytosis is reactive and responds to adequate iron therapy (8–10). Thrombocytosis secondary to iron deficiency at levels less than 1,000,000/cm^2 is considered benign, but serious complications, although rare, have been reported in iron deficiency anemia with platelet counts over 1 million (2, 3).

Although it is generally felt that a platelet count of over a million is necessary for hemorrhagic and thrombotic sequelae, the presence of relatively low levels of thrombocytosis, coupled with the stimulus of surgery, may have precipitated the massive intravascular thrombotic events leading to cerebral infarction and brain death in this patient.

This case suggests that a preoperative

finding of low-level thrombocytosis, in association with microcytic hypochromic anemia, should be evaluated carefully, since grave and fatal complications may occur following surgery, trauma, or other serious illness.

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Carcinoma of the Ureter with Isolated Lower-Extremity Swelling

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Abstract

An unusual case of transitional cell carcinoma of the ureter, the first reported case in which swelling of one leg was the only initial symptom, is presented.

Unilateral lower-extremity edema may be caused by venous insufficiency or obstruction or may have a lymphatic etiology, either primary lymphedema or lymphedema secondary to destruction or obstruction of normal lymphatic channels (neoplastic invasion, surgical excision, repeated infections, or parasitic infestation) or to radiation therapy (1).

This case report details a ureteral carcinoma that caused unilateral lymphatic and venous obstruction with none of the usual signs or symptoms of this disease process.

Case Report. A 74-year-old white man was admitted to the vascular surgery service for evaluation of a swollen, nontender left leg of 14 months' duration, after an abdominal computerized-tomography (CT) scan (Fig. 1) revealed a 4-cm left-lower-quadrant and pelvic mass compressing the left external iliac vein with no periaortic adenopathy.

On admission, the patient specifically reported not having abdominal or pelvic pain, change in bowel habits, bright-red blood per rectum, melena, nausea or vomiting, dysuria, hematuria, anorexia, weight loss, night sweats, or recent malaise.

His medical history was significant for myocardial infarction on three separate occasions, four-vessel coronary artery bypass graft two years prior to present admission, and a long history of hypertension. The patient reported that he had no history of gastrointestinal or genitourinary problems.

The patient appeared well; vital signs were normal. Head and neck were normal. No lymphadenopathy was palpable. Examination of the chest revealed clear lungs and normal heart. There was a well-healed midline sternotomy scar. Examination of the abdomen revealed a 4-cm mass in the left lower quadrant that was firm and slightly tender to palpation. Scrotal and penile edema was present. The prostate was symmetrically enlarged without palpable nodules. No extrarectal mass was palpated, and the stool was guaiac negative. The left leg showed 3+ chronic lymphedema without ulcers, gangrene, or tenderness. Neurovascular findings were normal, and flow was present in the proximal saphenous vein, as documented by Doppler study.

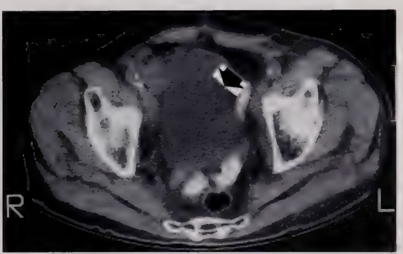

Fig. 1. CT scan showing 4-cm left-lower-quadrant and pelvic mass (arrow).

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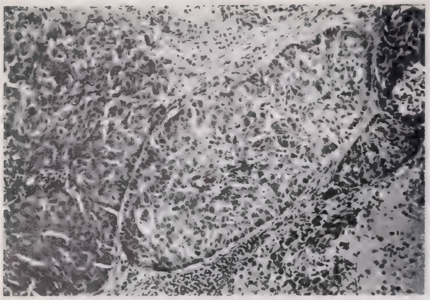

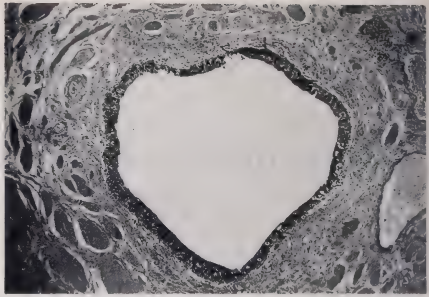

Fig. 2. **Left** Incisional biopsy showing transitional cell carcinoma (original magnification ×200).

Fig. 3. **Right** Chronic ureteritis with fibrosis and luminal narrowing of distal ureter. A few foci of poorly differentiated carcinoma in periureteral tissues are seen (original magnification 80×).

Laboratory data showed white-blood-cell count of 5,600/mm^3, hematocrit 39.5%. Clotting studies and serum electrolytes were normal. Urinalysis was normal without red blood cells. Acid phosphatase was 6.5 (normal values, 0.5–11). SMA-12 was normal. Chest x ray was normal, and electrocardiogram showed bifascicular block.

Incisional biopsy of the mass in the left lower quadrant showed poorly differentiated transitional cell carcinoma (Fig. 2). Intravenous pyelography (IVP) demonstrated minimal excretion on the left side, and although renal parenchyma could be seen, no excretion in the ureter was noted. No renal masses were seen. On cystoscopy, trilobar prostatic hypertrophy was noted. There was a tumor protruding from the left ureter; however, the ureter could not be cannulated for adequate biopsy. Prostatic needle biopsy was normal. Metastatic evaluation, including repeat CT scan, bone scan, and liver function tests, was negative. Venography revealed partial obstruction to flow through the external iliac vein.

The patient was then treated with 5,000 rad of external-beam radiotherapy, with marked reduction in the size of the mass and total resolution of his left-leg edema. Follow-up CT revealed a small residual mass in the region of the left hypogastric artery lying just outside the bladder wall. Metastatic evaluation, including bone scan, liver function tests, and chest x ray, was negative.

Left nephroureterectomy with partial excision of the pelvic mass and bladder cuff was performed. Exploratory laparotomy at that time was negative for extension to the liver or lymph nodes. Induration was palpable in the periureteral region extending to the pelvic side wall; however, the colon and small bowel mesentery were palpably free of tumor. Histopathologic examination revealed a few foci of poorly differentiated carcinoma in the wall of the distal ureter and periureteral tissues (Figs. 3, 4). There was no histopathologic evidence of tumor in the bladder, kidney, middle or proximal ureter, or submitted lymph nodes. The postoperative course was uneventful. Creatinine clearance with the solitary right kidney was 35 ml/min. Because of the patient's relatively good health with residual disease in the left pelvic side wall and poor prognosis with transureteral disease, cisplatin was administered at a dose of 50 mg/M^2/month for four months, with a repeat CT scan showing complete resolution of the residual mass.

Discussion. Primary carcinoma of the ureter is a relatively infrequent neoplasm, constituting approximately 1% of all tumors of the urinary tract (2–5).

Secondary involvement of the ureter may occur by direct implantation or dissemination of tumors arising from the kidney, bladder, or other neighboring structures or organs, or by hematogenous or lymphatic spread from distant sites. Histologically, tumors of the ureter can be classified into those of epithelial and those of mesodermal origin (6).

The etiology of primary ureteral carcinoma is obscure, although this tumor has been associated with workers in the dyestuff and leather-working industries, with patients with chronic urinary stasis, with bilharzial infections, phenacetin abuse, excessive coffee drinking, and heavy cigarette smoking (3, 7, 8).

The most common symptom is gross painless hematuria, occurring in approximately 75% of

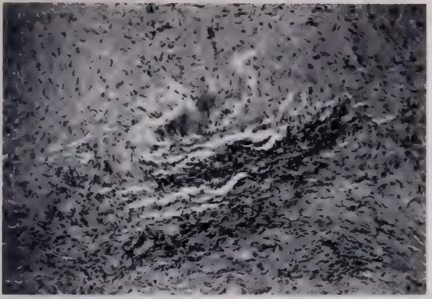

Fig. 4. Poorly differentiated carcinoma consistent with transitional cell type in periureteral tissue (original mangification 200×).

patients in one recent series. In the literature, gross hematuria has been associated with ureteral tumor in 75%–80% of cases, with flank pain in about 50% of patients, and with an abdominal mass (either a large kidney or lymph node mass) in about 30% of patients. IVP is a principal means of making the diagnosis (3–5, 7–9) and may demonstrate nonvisualization of the affected kidney in approximately 40% of the cases, as well as hydronephrosis and/or hydroureter. A ureteral filling defect is seen in a small percent of these patients. Because of the inability of an IVP to distinguish sessile and infiltrating neoplasms from metastic and nonneoplastic lesions affecting the ureter, other diagnostic modalities are often used, including retrograde pyelogram, retrograde brushings of ureteral lesions, and biopsies of the radiolucent areas (9).

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Fibrovascular Polyp of the Esophagus

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Abstract

Fibrovascular polyps of the esophagus are uncommon benign pedunculated tumors. Preoperative diagnosis of this lesion is essential for proper therapeutic planning. A case of a large fibrovascular polyp is reported in a 32-year-old male patient. Endoscopic and radiologic second opinions correctly diagnosed this mass, which resulted in a limited neck operation instead of the previously planned thoracotomy.

Pedunculated polyps of the esophagus are an uncommon cause of dysphagia. The correct diagnosis of this lesion is essential for proper therapeutic planning. We report a case in which endoscopic and radiologic second opinions diagnosed the true nature of an esophageal polyp, which resulted in a limited neck operation instead of the previously planned thoracotomy.

Case Report

A 32-year-old man with no significant medical history consulted his primary-care physician for complaints of dysphagia for 6 months. The patient's symptoms developed slowly, with the sensation of food "sticking" in the upper chest, more prominent with solids than liquids. There was no odynophagia or weight loss.

No abnormalities were revealed in physical examination or routine laboratory tests, including complete blood count, chemistry profile, and electrocardiogram. Chest x-ray demonstrated a left mediastinal soft tissue mass. X-rays revealed a dilated proximal esophagus with a huge mass, ending 10 cm proximal to the cardioesophageal junction. The patient had had two previous endoscopic examinations within several weeks, one of which revealed "multiple submucosal hard lumps." The mass was not considered to be pedunculated. Biopsies at that time were interpreted as revealing nonspecific inflammatory changes. A second endoscopic study demonstrated ulcerations at the distal end of the mass, and the biopsies were interpreted as "consistent with fragments of fibrovascular polyp."

The patient was referred for a second opinion. In the physician's office a third upper-intestinal endoscopic examination was performed. Just beyond the cricopharynx, there appeared to be a fairly narrow pedicle from which a large mass was suspended, filling the esophagus. Retained food was present within the esophagus. The mass extended to the midesophagus. The distal end was friable and ulcerated. The remainder of the esophagus, stomach, and duodenum were normal. Upon withdrawal of the endoscope following gastroscopy, it was apparent that the mass moved independently of the esophageal wall, was not fixed to it, and was not submucosal. Biopsies taken from the distal end of the mass showed chronic inflammation and fibrosis.

Subsequent radiographic examination of the esophagus (Fig. 1) was performed to confirm the intraluminal nature of the mass as well as to further delineate its site of attachment. A 25-cm-long lobulated mass was demonstrated with attachment at the level of the cricopharyngeus. A diagnosis of fibrovascular polyp of the esophagus was made radiographically.

The patient was subsequently admitted to the hospital for surgery. Because it was known that the pedicle was attached high in the cervical esophagus, the tumor was removed through a left

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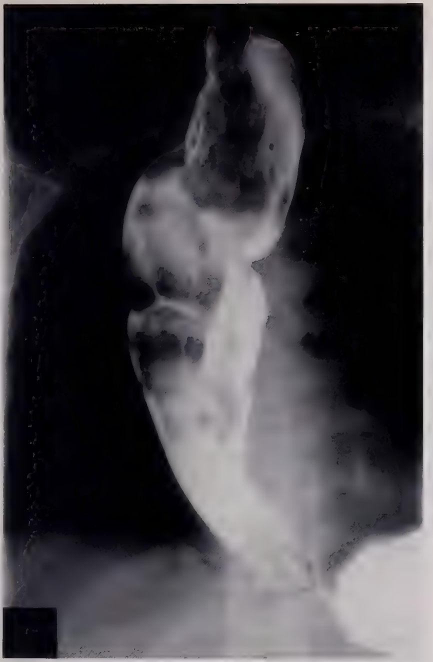
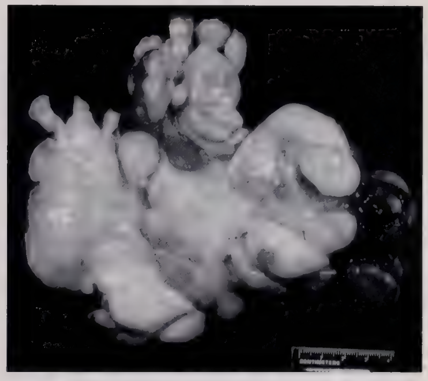


Fig. 1. Barium swallow shows dilated esophagus with large intraluminal lobulated mass. Cineesophogram demonstrated site of attachment near cricopharynx.

Fig. 2. The 28.5-cm polyp was soft and lobulated with areas of ulceration. Microscopic evaluation showed it to be a fibrovascular polyp.



lateral pharyngotomy. The stalk was sutured and divided, the polyp being pulled out of the intact esophagus. The size of the tumor required placement of a temporary tracheostomy. The postoperative course was complicated by right-lower-lobe pneumonia, treated successfully with antibiotics. The patient was discharged two weeks after admission and remains symptom free.

Pathologic examination confirmed the diagnosis of a fibrovascular polyp (Fig. 2).

Discussion

Fibrovascular polyps are the second most common benign tumor of the esophagus and the most common benign pedunculated polyp of the esophagus (1). These tumors characteristically do not produce symptoms while growing to an extremely large size (2). The lack of dysphagia is related to the softness of the tumor, causing it to be compliant rather than causing obstructive symptoms (3). In this patient the polyp grew to almost 1 ft in length (28.5 cm). Fibrovascular polyps are characteristically slow-growing, solitary tumors that commonly attain sizes in excess of 10 cm before becoming symptomatic; 75% of these polyps are greater than 7 cm at the time of diagnosis. Regurgitation of the polyp may result in asphyxiation, a rare complication (1).

Endoscopic and radiologic studies and performance of a cervical esophogram are important preoperative evaluations. In this patient, both the tertiary endoscopist and the radiologist properly identified a pedicle in the cricopharynx; this extremely important information had a tremendous impact on the approach to surgery. In this patient, knowledge of a stalk attachment allowed ease of removal through a lateral pharyngostomy rather than the planned thoracotomy.

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Isolated Tongue Hemiatrophy

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Abstract

Three patients with hemiatrophy of the tongue are described. All three had difficulty chewing and swallowing food, speech slurring, and occasional tongue biting. Associated illnesses included hypertension in two and diabetes in one. In all patients, the left half of the tongue was atrophic, without gross fasciculations. Sensation to pinprick and taste were preserved. Other bulbar nerve function was normal. Normal laboratory examination included CT scan (all), tomograms of the base of the skull (two), and four-vessel cranial angiography (one). Electrodiagnostic studies in all three documented denervation of the atrophic half of the tongue with some preserved volition. The blink reflex, motor latency to facial and sternocleidomastoid muscles, and electromyography of the temporalis, facial, soft palate, and sternocleidomastoid muscles were normal. There was no evidence of peripheral polyneuropathy. Follow-up for ten years of one patient and more than three years of two patients revealed no change.

Isolated nonprogressive hemiatrophy is benign and is probably caused by a discrete lesion of the hypoglossal nucleus. This site is presumptive in the absence of confirmation at autopsy.

The literature contains numerous reports of hypoglossal hemiatrophy associated with various conditions, but only a few reports of isolated tongue hemiatrophy.

The purpose of this communication is to describe three such cases to report on the electrodiagnostic findings and to discuss possible etiologies and prognosis. Hypertension is known to cause brain-stem lacunar infarcts; an association with hypertension is present in two of these three cases.

Case Reports

Three patients, one man and two women, ranging in age from 46 to 77 are described.

Independent neurologic examinations were performed by each author, documenting that tongue atrophy was the only cranial nerve abnormality present. Electrodiagnostic studies consisted of electromyographic sampling of facial muscles (nerve VII), temporalis (nerve V), soft palate (nerves IX, X), sternocleidomastoid (nerve XI), and tongue (nerve XII) using concentric needle electrodes. Facial nerve latencies and blink reflexes were measured using standard techniques (1).

Peripheral function was also evaluated. This consisted of electromyographic sampling of proximal and distal muscles of the upper and lower extremities. In addition, conduction studies were performed using standard techniques (1). These included motor studies, sensory nerve studies, F waves, and H responses. Follow-up ranged from three to ten years.

Case 1. A 77-year-old woman reported a two-year history of persistent left occipital headaches with occasional dizziness and blurred vision. The patient noted difficulty in moving her tongue and shifting food in her mouth, as well as occasional swallowing difficulties.

Her medical history included hypertension, heart disease, and diabetes, all under good control, and an old partial thyroidectomy.

Neurologic examination showed mild ptosis of the left eye and presbyacusia. The left side of

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the tongue was atrophic and the tongue deviated to the left. Other bulbar nerves were normal. Strength in the right hand was decreased (she had documented carpal tunnel syndrome). All other neurologic findings were normal; neck movements were free; no tenderness of skull was detected. No masses were noted in the neck. Skull series, tomograms of skull base, bone scans, and CT were all normal. Laboratory data excluded vasculitis or blood dyscrasia.

EMG of the tongue revealed fibrillation potentials and positive sharp waves of the left half with preserved motor unit potentials. Other cranial nerves, including V, VII, IX–X, XI, tested normal. Nerve conduction studies were normal.

Three years later, her headaches have subsided considerably. She still has occasional difficulty swallowing and chewing, and her speech is still slurred.

Case 2. A 46-year-old hypertensive man had severe vertex headache of recent onset, forgetfulness, and decreased job performance. This was followed by difficulty with speech, tongue movement, chewing, and swallowing.

Examination revealed atrophy of the left side of the tongue with deviation to the left on protrusion. Pinprick response and taste were normal. The left jaw appeared lower. Other bulbar muscles were not involved, and other neurologic findings, including routine mental status test, were normal. There were no masses on palpation of the neck.

EMG of the tongue showed fibrillation potentials and positive sharp waves at rest, and volitional motor unit potentials on the left side. Cranial nerves V and VII were normal. There was no electrical evidence of polyneuropathy by nerve conduction studies. Skull x-ray, brain scan, Doppler studies of carotids, and CT scan were all normal. Three years later, the patient is well and working. His condition has not changed.

Case 3. A 51-year-old otherwise healthy woman was evaluated for atrophy of the left hemitongue, present for at least three years.

The patient had noticed gradual shrinking in tongue size. On examination she denied currently having speech, chewing, or swallowing difficulty; all had been initially present. The left half of the tongue showed moderate atrophy. Pinprick response and taste were preserved. Other neurologic findings and cranial nerves were normal. The oral cavity was normal except for upper dentures. The results of carotid auscultation bilaterally, an aortic arch study, and routine laboratory studies, including serology, were normal.

Over the ensuing ten years, the patient's tongue atrophy did not progress. She has not had difficulties with speech or swallowing, and other neurologic findings have remained normal.

Nerve electromyography confirmed fibrillation potentials, positive sharp waves, and volitional motor unit potentials in the left half of the tongue. Other cranial nerves, including V, VII, IX–X, XI, and nerve conduction of limbs were normal.

A CT scan of the head in 1981 was normal. Ten years after the onset of symptoms, she is well and working.

Discussion

Among reported causes of hemitongue atrophy, tumors of the hypoglossal nerve may cause isolated tongue hemiatrophy (2, 3). Often other findings, such as Horner's syndrome (3) and long tract signs (4), followed by multiple ipsilateral involvement of cranial nerves and eventually increased intracranial pressure, are present (5–8). Diagnosis is made by CT, which will outline the hypoglossal nerve tumor, and Stenvers views, which show enlargement of the hypoglossal canal.

Instances of isolated hemiatrophy have been reported with metastatic carcinomas (9), clivus plasmacytoma (10), and glomus tumors (11), but in all cases metastatic cancer had already been diagnosed and in no patient was the tongue atrophy an initial symptom. Moreover, the tongue atrophy was rapidly followed by involvement of other cranial nerves, often ipsilateral.

Iatrogenic isolated hypoglossal hemiatrophy has been reported after carotid endarterectomy (12) and radiation therapy (13, 14). Vascular etiologies include entrapment by a tortuous internal carotid artery (15) and hypoglossal nerve penetration of the vertebral artery (16).

Finally, isolated tongue hemiatrophy has been reported after influenza vaccination (17), infectious mononucleosis (18), and in one case, with no established etiology (19).

Although electrodiagnosis in cases of isolated tongue hemiatrophy has been performed, it was restricted to study of the hypoglossal nerve (19, 20). Other cranial nerves were sampled electromyographically in the case of vascular entrapment in the neck (15). No peripheral studies were ever reported.

In our cases, the clinical impression of pathology restricted to the hypoglossal nerve gained support from the electrodiagnostic findings: denervation was present in only one-half of the tongue. In all three cases the electrodiagnostic abnormalities were restricted to fibrillation potentials and positive sharp waves in the atrophic half of the tongue only. No peripheral findings were present except in case 1; that patient had carpal tunnel syndrome. Further electrodiagnostic evaluation of cranial nerves V, VII, IX–X, and XI documented normal, intact function. Similarly, nerve conduction and EMG performed for possible polyneuropathy (in three cases) and myopathy (in two cases) were negative.

The neurologist should be particularly concerned with the possibility of metastatic neoplasm at the base of the skull (21) causing isolated tongue hemiatrophy or a hypoglossal nerve sheath tumor. If the atrophy is isolated, if there is no history of cancer, and if the CT scan is normal, the condition can be considered benign. If involvement of other cranial nerves occurs or follows, a neoplasm of the base of the skull must be ruled out (21).

In malignant conditions, progression has almost always been evident within a few weeks or months. Skull x-rays with Stenvers views and tomograms of the base of the skull are of value in diagnosis. In difficult cases, examination of the cerebrospinal fluid for evidence of carcinomatosis may be helpful.

In our patients, the condition has remained isolated and nonprogressive to date. The site for such a restricted lesion is probably in the nucleus of nerve XII or in the medulla oblongata along its fibers. The latter site is less likely with a normal CT and lack of erosion at the base of the skull.

In case 1, the patient with diabetes and hypertension, small lacunar infarcts in the medulla might have been the cause. In case 2, the patient was also hypertensive, and a similar etiology may be invoked. In case 3, hypertension was not present. Infectious etiologies were excluded by history, and arterial abnormalities by angiography. Of course, a single vascular lesion such as a small arteriovenous malformation could have affected the hypoglossal nucleus proper in the medulla. Such lesions, however, are usually associated with contralateral hemiparesis (22, 23).

Therefore, considering the isolated nonprogressive nature of the findings and the EMG findings consistent with lower motor neuron disease, we conclude that the lesion was small, probably in the medulla and affecting the nucleus of the hypoglossal nerve. Isolated nonprogressive tongue hemiatrophy documented by electromyography is a benign lesion not requiring extensive workup.

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Osteochondrosarcoma of the Sternum: 29-Year Cure by Radical Surgery

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Abstract

A case of osteochondrosarcoma of the sternum was first diagnosed in a middle-aged woman and treated surgically in 1943. Following a number of surgical procedures for recurrences, definitive surgery, including excision of gladiolus and xiphoid of sternum cartilages and segments of ribs, was performed in 1958. In mid-1987 this female patient was 88 years of age, free of disease and without respiratory difficulties. No prosthetic material or muscle transplants were employed to close the defect or stabilize the chest wall; however, both breasts were mobilized and brought together in the midline to assist in closing the defect.

Three recent articles dealing with chest wall tumors involving sternal resection prompted me to report this unusual case. One article dealt with muscle transposition and pulmonary function (1), another with chest wall tumors (2), and a third with thoracic wall defects (3).

Case Report

A woman, aged 43 years, was referred to Dr. Harold Neuhof on 1/28/43 and was operated on for a clinical picture of an inflammatory lesion of the anterior chest wall. The lesion turned out to be a neoplasm involving the thoracic parietes and parietal pleura. There was also invasion of one vein. Operation in January 1943 consisted of a wide excision of tumor, including several ribs and parietal pleura.

The pathology report was chondrosarcoma. That report was as follows: specimen consists of segments of two ribs and a tumor mass adherent to the internal surface of one of the ribs. On the dorsal surface the ribs present nothing unusual. There is adherent muscle and connective tissue. On the anterior surface there is a bulging, firm tumor mass approximately oval in shape, 5.5 × 4.5 cm. It has been incised in several places, is discolored by blood and dried. It is firm in the upper portion, somewhat cystic in the lower portion. The external surface is white with yellow streaky and hemorrhagic discoloration. Cross section shows the upper portion to be firm, white, and resistant and the lower portion to be broken down, hemorrhagic, and partly gelatinous. It is intimately adherent to the underlying rib, which has only been removed from the middle of the tumor in one direction, 5 cm long. The other rib, which does not appear adherent to the mass, measures about 12.5 cm. Cross section of the rib at the end of resection underlying the tumor shows an area which is soft, somewhat crushed, and either the site of tumor or trauma in removal.

Radiographic studies made September 1943, December 1943, April 1945, January 1946, and May 1946 revealed resection of the fourth and fifth right ribs anteriorly and no evidence of recurrence.

Events of 1952. The patient was referred to me by Dr. H. Neuhof. One month prior to this referral, the patient had noted a sensitive area over the right border of the sternum which was swollen but not inflamed. I performed surgery on 9/23/52 for recurrent or persistent chondrosarcoma of the chest wall.

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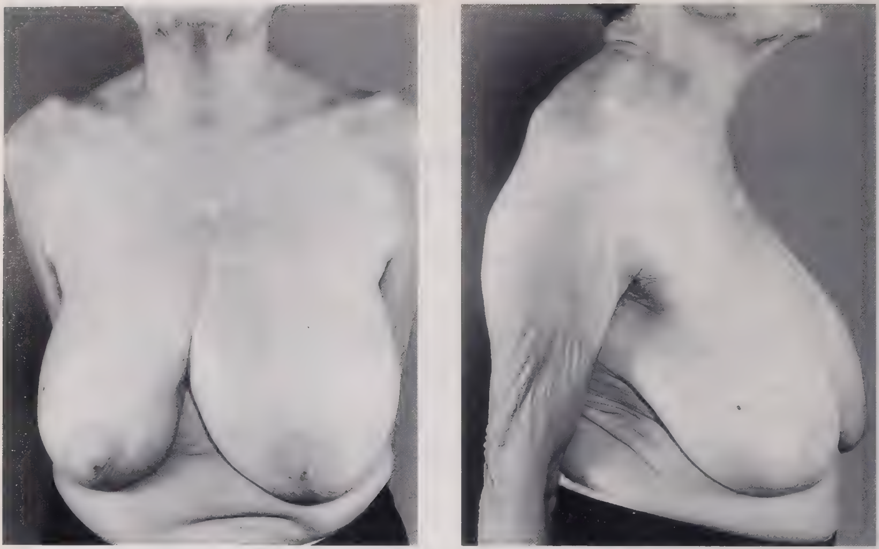

Fig. 1. Status at 12/22/86 of postoperative area of chest; anterior (**left**) and lateral (**right**) views.

There was a tumefaction in the region of the third(?) costal cartilage, which was tender and had increased in size over a period of at least a month. The previous incision was partially excised and the incision extended upward toward the neck so as to freely liberate the breast and the anterior flap. The pathologic area was easily identified and a section was taken which proved to be a sarcoma on frozen section. Therefore, the cartilage itself was excised, plus a segment of cartilage and rib above; the pleural cavity was then easily visualized and entered. There was no evidence of pleural metastases and the lung appeared to be soft, although it was completely adherent in this area. The mediastinum seemed to be free. About a third of the sternum on this side was resected in an elliptical manner so as to be sure that no evidence of sarcoma was left in the patient's chest. At the termination of the operation there was a considerable defect in the chest wall, closed partially by muscle and facial suture, partially by subcutaneous adipose tissue approximation, and partially by skin alone. The breast was brought back to its original position. Due to some oozing in the region of the sternal resection, Gelfoam was placed over the oozing area and left in situ. No drains were employed; silk technique was used throughout. The patient's condition remained good throughout the procedure.

The pathology report was chondrosarcoma; small fragments of bone were also found.

Follow-up was uneventful for three years; in 1955 a recurrence was noted involving the sternum.

Events of 1955. On 9/9/55 a segment of sternum with attached muscle, fat, and a narrow strip of skin was excised with costal cartilage. The sternum segment was 6.5 cm in length and approximately 4 cm in greatest width. Both ends of the sternum showed the usual trabeculated bone marrows. On one side were resected costal chondral junctions of three ribs. The other side was covered over with fibrous tissue and did not show articulations. On sectioning the sternum, the marrow was largely grayish-tan, slightly gelatinous in appearance in some areas, and easily broken. Near one line of resection of the sternum was some cartilage, probably representing the manubriogladiolal junction. This sharply delimited the extent of tumor. At the lower end of resection, there was no clear demarcation of normal and involved marrow. In the anterior surface of the sternum were 2 small cystic-appearing structures containing gelatinous material in the peri-

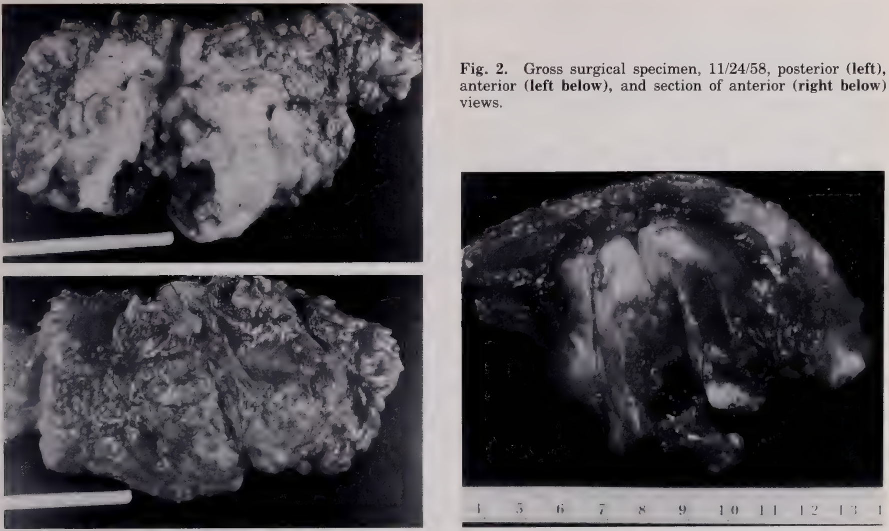

Fig. 2. Gross surgical specimen, 11/24/58, posterior (**left**), anterior (**left below**), and section of anterior (**right below**) views.

osteum. The attached muscle and fat tissue showed nothing unusual. The elliptical piece of skin measured 7 × 1 cm and had a linear scar down the middle. Two separate segments of cartilage, one 3.5 cm and the other 2.5 cm, were connected by intercostal muscle.

The pathology report identified recurrent chondrosarcoma involving the sternum, and noted that the resected edge was free of tumors, and that the costal cartilage received separately showed no evidence of tumor.

The patient's postoperative course was good. Follow-up remained uneventful until November 1958, when a recurrence of the tumor was noted, involving the remaining portion of the sternum and segments of ribs on either side.

Events of 1958. On 11/24/58 I performed resection of recurrent sarcoma of the anterior chest wall and mediastinum.

The previous midline incision over the sternum was excised and extended bilaterally as a submammary incision on either side. Skin was dissected away from the large mass, and the mass itself appeared to be well encapsulated. This mass went down to the pericardium and pleura but did not involve the pleura and also extended at the lower angle down toward the rectus sheath. Part of the rectus sheath was excised; the rectus muscle was excised en masse, as were segments of two cartilages on the left side which appeared to be involved. At the end of the dissection the entire mass was removed. Both pleural cavities were visible, as was the entire anterior surface of the pericardium. Neither pleural space was entered. Hemostasis was accomplished without too much difficulty.

To partly close the large space, the two breasts were brought together by several subcutaneous sutures in the midline. The skin was then closed (Fig. 1) and drains were placed both in the main wound and laterally into the extension.

Specimen (Fig. 2) included a segment of sternum 6.5 cm long with xiphoid and four short segments of ribs on each side. The external surface was covered by a large amount of adipose tissue, muscles, and fibrous tissue. The upper half of this specimen showed a large bulging mass 8 cm in greatest diameter which on section was multicystic. The lumina of the cyst contained a large amount of clear and blood-tinged mucinous material. All the cysts were lined by soft and friable white gelatinous papillary regular and flat growths. The corresponding portion of sternum and ribs were invaded and destroyed by tumor tissue. The pathology report showed osteochondrosarcoma of rib infiltrating sternum.

Repeated reexaminations and radiographic studies failed to show any evidence of recurrence of the chondrosarcoma.

Events of 1963. The report on radiographic studies performed 10/15/63 was as follows:

The dorsal spine shows moderate hypertrophic lipping and spurring on the anterior and lateral articular angles of the dorsal vertebral bodies. The appearance is that of mild hypertrophic arthritis. No intrinsic osseous disease or metastasis is observed in the dorsal spine. The bones appear normal. The intervertebral and interpedicular spaces are normal.

The ribs and sternum again show postoperative status following resection of the right fourth and fifth ribs anteriorly as well as the body of the sternum. Minimal calcifications in the soft tissues characteristic of postoperative recalcification are observed in this region. There is no characteristic evidence of a soft tissue mass or extension of the previous neoplasm to the manubrium or adjacent ribs.

All the ribs appear normal except for the surgical defects of the right fourth or fifth ribs. There is no evidence of metastasis.

Events of 1970. The patient was referred for neurosurgical studies because of headaches she had suffered for the last fifteen years. Roentgenograms of the skull showed an area of calcification to the right of the midline in the posterior parietal area. The impression was calcification of the dura or calcification in a meningioma. A brain scan confirmed a diagnosis of meningioma, not symptomatic. The recommendation was that no treatment was required at the time.

Current Status of Patient. Headaches still occur rarely and respond well to acetylsalicylic acid medication.

Discussion

During radical surgery to treat this rare pathologic entity it is imperative to employ frequent frozen section controls to insure removal of all tumor with a wide margin. Entry into the pleural cavity or pericardial sac should be avoided unless those sites have been invaded by the neoplasm. Closure of the defect may require improvisation to insure chest wall stability and preserve pulmonary function. Last but not least, one must insist on regular follow-ups to examine for distant metastases or a local recurrence. Any local recurrence should be excised if feasible, and follow-up should continue during the life of the patient.

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The Association of Papilledema with Syringomyelia: Case Report

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Sun Kyu Song, M.D., Joseph W. Eichenbaum, M.D., and Martin B. Camins, M.D.,

Abstract

A 54-year-old woman with classic signs, symptoms, radiologic evidence, and autopsy findings of syringomyelia and syringobulbia is described. During the course of her illness the patient developed papilledema without hydrocephalus. This has not been previously described in the literature.

In 1546, Estienne (1) described cavitations of the spinal cord. Since that time the entity of syringomyelia and syringobulbia and its classic constellation of signs and symptoms have been well described.

The first reported case of syringomyelia and papilledema was described in 1896 by Saxer (2). Since that time, syringomyelia has been noted to be an infrequent cause of papilledema (3, 4). Detailed radiologic evaluation of these patients has always disclosed an internal hydrocephalus with an associated anomaly of the posterior fossa. This report describes an exceptional case of syringomyelia and papilledema without hydrocephalus.

Case Report

In 1975, when she was 54 years old, an asthmatic, hypertensive, diabetic, obese woman burned her left arm, without any awareness of pain. Not until the following year, when she developed a "bulging" of the left shoulder, did she seek medical attention. She also noted decrease in power and impaired range of motion in the left shoulder. A pantopaque myelogram and EMG done at that time were nondiagnostic. Orthopedic evaluation and subsequent surgical findings were consistent with a Charcot joint.

Routine follow-up examinations disclosed no deterioration in her condition until August 1982, when she suddenly developed pins-and-needles paresthesias in her left upper extremity extending from the elbow to her left hand. Two days later she awoke with numbness on the left side of her body from her shoulder to her toes. She was hospitalized.

Her neurologic examination was significant for a left hemiparesis with atrophy of the left upper extremity, bilaterally decreased pain sensation from C5 to T10 except for a preserved band on the right from T2 to T4, decreased vibration to the knees, decreased deep tendon reflexes (DTR) in the upper extremities, increased DTR in the lower extremities, and bilateral Babinski signs. The patient had difficulty walking unaided, which was ascribed to her left hemiparesis. The patient's fundoscopic examination at this time was normal. A metrizamide myelogram (Fig. 1) and postmetrizamide CT scan of the spine (Fig. 2) as well as gas myelography (Fig. 3) were performed. The finding of a widened cervical and thoracic cord, with the presence of a collapsible cyst, was felt to be consistent with a syrinx. No evidence of an Arnold-Chiari malformation was seen.

Over the next five months the patient's left side became progressively weaker and she developed dysesthesias of the right hand. Constipation

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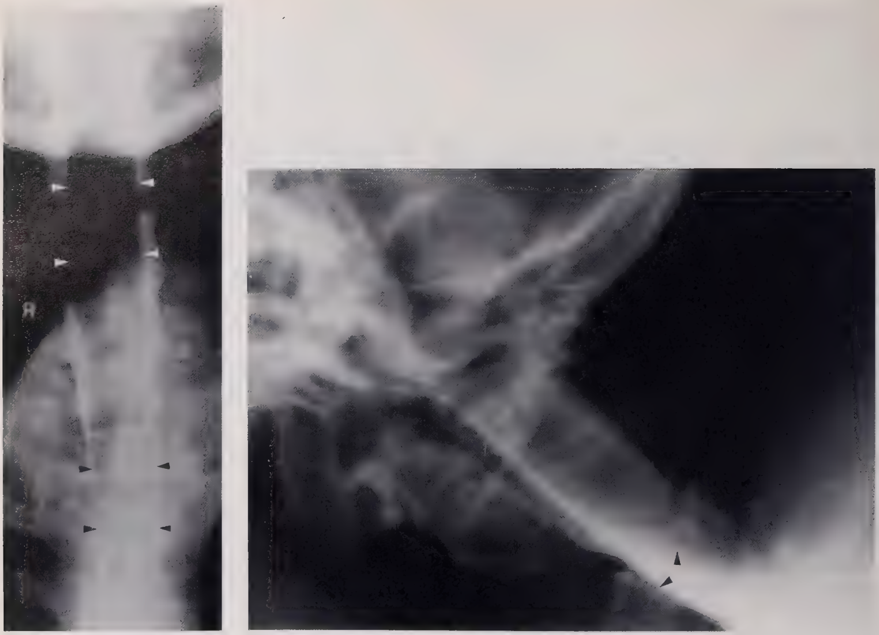


Fig. 1. Metrizamide myelogram. **Left** Posterior-anterior view; cord shows enlargement in cervical (white arrowheads) as well as thoracic (black arrowheads) area. **Right** Lateral view; collapsibility of syringomyelic cavity is suggested by settling of metrizamide in dependent anterior cervical cord (black arrowheads).

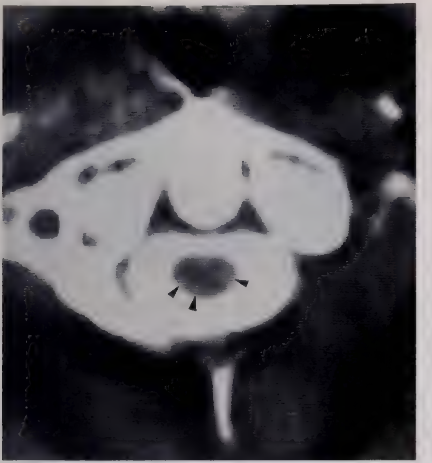
but no change in bladder habit was noted. Further weakening of her left side and increasing dysesthesias of her right hand prompted a trial of steroid treatment. She was readmitted in February 1983. Repeat myelography and a CT scan of the spine remained consistent with a cervicothoracic syrinx. Cerebrospinal fluid studies, including the opening pressure, were normal. While in the hospital the patient suffered a second-degree burn on her right arm while leaning on a radiator without any awareness of the heat. The steroids were tapered during the month of February 1983 because they seemed to have little palliative effect.

In March 1983, ophthalmologic examination now revealed papilledema, and there was further deterioration in her strength and paresthesias. This was the first time the patient's fundi showed evidence of increased intracranial pressure. The patient was rehospitalized as an emergency. The patient adamantly denied any headache or visual complaints. Her profound obesity and weak legs made it difficult for her to walk even with a cane or walker.

Ophthalmologic examination disclosed blurred optic disc margins with an increased blind spot but preserved visual acuity, and gaze-directed nystagmus on lateral gaze with an occasional rotary component.

Neurologic findings were hemiatrophy of the left side of the tongue, a four-fifths triparesis of the right and left lower extremity and left upper extremity, a capelike loss of pinprick and temperature sensation, and decreased vibratory sensation in the arms, more prominent distally than proximally. Her deep tendon reflexes were absent in the upper extremities and brisk in the lower extremities. Babinski's sign was present bilaterally.

Laboratory studies disclosed a mild hypochromic, microcytic anemia. The CT scan of the patient's brain was normal, including normal-sized ventricles. Fluorescein angiography and retinal photographs were consistent with papill-



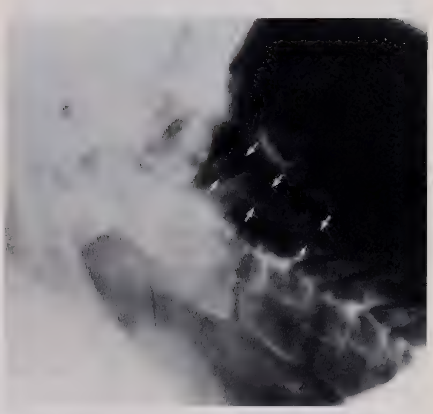


Fig. 2. **Left** Postmetrizamide CT scan of spine. Upper end of cervical cord. Note presence of contrast material within spinal cord parenchyma. Black arrows delineate small areas of contrast within irregular syringomyelic cavity. **Fig. 3.** **Right** Air myelogram, lateral view; upper cervical region. Rows of white arrows delineate anterior and posterior borders of collapsed upper cervical cord.

edema (Fig. 4). She was again treated with steroids (dexamethasone 4 mg three times a day) and her papilledema gradually resolved. There was some minimal improvement in other aspects of her condition referable to the syrinx.

The patient was discharged on a regimen of tapering doses of steroids. Three days after decreasing her daily dexamethasone dose from 12 mg to 10 mg, the patient developed increasing gait difficulty and recurrence of the papilledema.

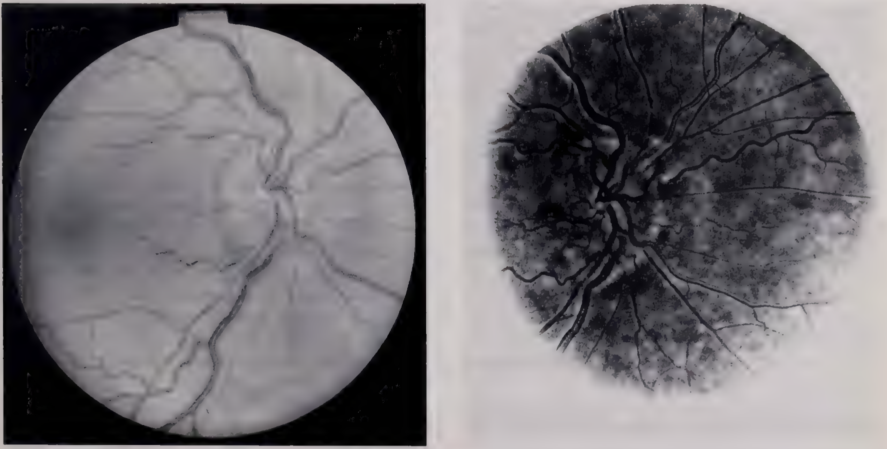


Fig. 4. **Left** Retinal photograph, OD. Blurred disc margins, venous suffusion and obliteration of cup are present. **Right** Retinal angiogram, OD, mid-late venous phase. Peripapillary leakage of fluorescein around blurred disc margins is consistent with diagnosis of papilledema.

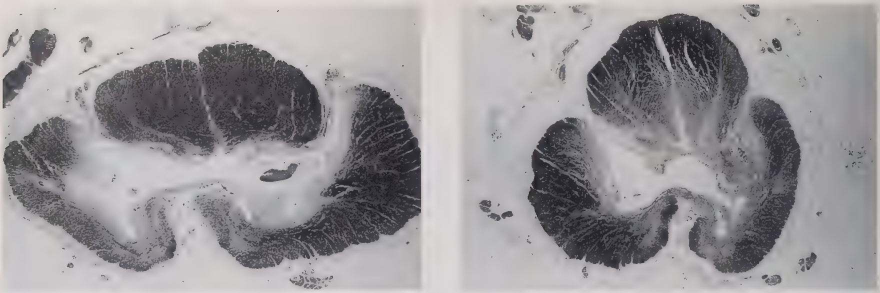


Fig. 5. Left Transverse section of lower cervical cord (Kluver stain). Syringomyelic cavity is well demonstrated. A channel communicating with subarachnoid space in area of left dorsal root region can be seen. **Fig. 6. Right** Transverse section through mid-thoracic cord (Kluver stain). Glial-lined syringomyelic cavity is seen.

A lumbar puncture was performed with an opening pressure of 140mm H_2O. The Queckenstedt maneuver created an immediate rise in pressure to 350; unilateral pressure (Tobey-Ayer test) also brought a prompt rise in pressure to approximately 340, with quick restoration to the normal opening pressure upon release. The cerebrospinal fluid was normal except for a protein level of 0.57g/L. Digital venous imaging was also normal. Surgical approaches to the patient's syrinx were reconsidered but deferred because of the high risk in this patient.

In June the patient appeared at The Mount Sinai Hospital emergency room hypotensive, hypothermic, with crepitus, tenderness, and erythema of the right lower extremity and a bullous lesion of the right calf. It was determined that she was suffering from gas-gangrene and gram-negative sepsis. Cultures from aspiration of the right lower extremity grew *Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus faecalis,* and *Enterobacter cloacae*.The patient died and an autopsy was obtained.

Autopsy Findings. A general postmortem examination performed approximately 7 hours after death revealed an acute bronchopneumonia and minimal valvulitis of the tricuspid and mitral valves with marantic endocarditis of the tricuspid. Death was attributed to sepsis by anaerobic bacteria associated with extensive gas-gangrene of the right lower extremity. The eyes were not examined.

The findings in the nervous system consisted of two separate syringomyelic cavities in the cervical (Fig. 5) and thoracic spinal cord (Fig. 6). The rostral extreme of the upper syrinx was situated in the left dorsolateral quadrant of the medulla containing the rostral end of the olives and the hypoglossal nuclei. The cavity ended abruptly at the level of C-8, and the lower syrinx starting from the level of T-3 extended caudally to involve the entire length of the thoracic cord. The lumbar spinal cord and below were intact. Both syrinx cavities were glial-lined and had communications with the subarachnoid space. The syringomyelic cavities contained a large amount of fresh blood, as did the subarachnoid space. The source of the hemorrhage could not be determined. The cerebral hemispheres, cerebellum, and midbrain and pontine portions of the brainstem disclosed no abnormalities. There was no evidence of hydrocephalus. There was no evidence suggesting Arnold-Chiari malformation, neural bands in the posterior fossa, or chronic arachnoiditis. The basal foraminae of Magendie and Luschka were grossly intact.

Discussion

Syringomyelia is a well-known entity with characteristic clinical signs and symptoms. Barnett has concluded that syringomyelia "can be regarded as a generically useful word referring to several nosologically distinct forms of extending spinal cord cavitation" (3). Because our patient demonstrated the classical clinical signs and symptoms, a flaccid cyst at gas myelography, and a spinal cord cavitation lined by glial elements on microscopic examination, it appears that this case fits the criteria for classification as syringomyelia. The physical findings of dissociated sensory loss, muscular weakness and wasting of the upper extremities, long tract signs in the lower extremities, arthropathy and trophic changes correlate with the autopsy findings of spinal cord cavitation from C1 to T2 and from T3/4 to T12.

The clinical finding of a bandlike area of preserved pain sensation along the right T2-4 region (noted transiently in summer 1982) can be associated with the sparing of the patient's spinal cord from T1 to T3. Rostral ascensions within the zone of Lissauer and the substantia gelatinosa of pain-carrying fibers, prior to decussation, have been invoked to explain discrepancies between clinical dermatomal findings and pathologic processes. In addition, her nystagmus and hemiatrophy of the tongue, and the cavitation in her medulla at autopsy, suggest that she suffered from syringobulbia as well.

The occurrence of syringomyelia with papilledema is well-known (2, 5) but rare enough not to be often mentioned in large series of syrinx patients (6, 7). In 1931, Alpers (4) wrote a landmark paper reviewing four prior case reports as well as presenting his own case of "syringomyelia with choked discs." He concluded that "the cause of the choked disc was found to be an internal hydrocephalus secondary to a closure of the foramina in the roof of the fourth ventricle." His conclusion has been well accepted, and no prior reports of syringomyelia and papilledema without hydrocephalus have appeared.

Our radiologic and autopsy studies demonstrated some very significant findings in this patient: metrizamide within the spinal cord, fourth ventricular outlet patency, absence of an Arnold-Chiari malformation, and no neural bands, cysts, or arachnoiditis in the area of the foramen magnum. These observations reflect somewhat on previously proposed pathogenetic mechanisms of a syrinx. Gardner's hydrodynamic theory presupposes some developmental delay or inadequacy in the opening of the basal foramina (8). Although in this case no obvious hindrance to normal CSF flow was disclosed, we must, of course, accept the possibility that obstruction to the normal flow of CSF can occur at other stages in a patient's life or intermittently with the assumption of various head positions. Nonetheless, if we wish to attempt a unified explanation for the findings in our patient's case, gross obstruction of the basal foramina or any valvelike mechanism from a hindbrain anomaly seems unlikely (8, 12).

It is possible that this patient suffered from two separate maladies: syringobulbia-syringomyelia and pseudotumor cerebri. These two entities, though, have never previously been associated with each other. Yet when syringomyelia is associated with obstructive hydrocephalus, it may lead to increased intracranial pressure and simulate pseudotumor (3, 14). What argues against the possibility of our patient having pseudotumor cerebri is her denial of headaches and visual problems, and a normal opening pressure at the time of lumbar puncture. Also of note is the finding of normal and not slitlike ventricles on CT scan (a variable finding in pseudotumor), her age (occurrence of pseudotumor after 50 is rare), and the slightly elevated CSF protein (low CSF protein has been seen in pseudotumor) (13, 14). With a normal digital subtraction angiogram and unilateral Queckenstedt maneuver (Tobey-Ayer test), the diagnosis of a sinus thrombosis as the cause of pseudotumor cerebri is unlikely.

In support of the diagnosis of pseudotumor cerebri is the temporal relations of steroid withdrawal to the occurrence of papilledema and its reappearance with tapering of the dose. Other known causes of pseudotumor that may have played a role in this case were the patient's obesity and anemia. An increased blood flow and volume with anemia (usually with severe anemia) is the presumptive mechanism in the rare case of pseudotumor associated with anemia (15). Because our patient's anemia was quite mild (hemoglobin 6.8 mmol/L, hematocrit 0.354), I doubt that this factor contributed significantly to her fundoscopic findings. The appearance of papilledema both times the steroids were tapered provides strong evidence that a steroid-withdrawal-induced pseudotumor cerebri may have been occurring. As for the absence of headaches, pseudotumor without headaches has been mentioned in the literature before (16).

To postulate how a syrinx may alter the course of pseudotumor: the new fluid reservoir afforded by the syringomyelic cavity may inhibit the full expression of elevated intracranial pressure, clinically manifested by headaches or visual complaints. Conversely, an increase in intracranial pressure may promote the cavitation process and explain the exacerbation of our patient's symptoms, referable to her syrinx, concomitant with the development of her papilledema.

Summary

Although it is probable that this patient suffered from two separate maladies that may each have influenced the other's expression, it is tempting to hypothesize that a single, poorly understood process was responsible for all the findings. The purpose of this case report is to present for the first time the association of syringomyelia-syringobulbia with papilledema which

is unique for the absence of internal hydrocephalus.

Alternatively, this case may represent a unique association of syringomyelia with pseudotumor cerebri.

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Ewing's Sarcoma Arising in the Sacral Epidural Space: Case Report

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Abstract

The case of a 33-year-old woman with primary epidural sarcoma mimicking lumbosacral disk herniation is reported. The neuroradiologic studies, surgical intervention, histopathologic sections, and chemotherapeutic management are discussed. A brief review of the five cases previously reported in the literature is presented.

Tumors found in the spinal epidural space are usually metastatic carcinomata (1). The most common primary spinal epidural neoplasm is lymphoma (2). Ewing's sarcoma of bone is an undifferentiated round-cell sarcoma most often found in the metaphysis of a long bone, in males, and in the first two decades of life (3). Ewing's tumor arising in the spinal epidural space has previously been reported only five times in the literature (4–6). The rarity of this epidural neoplasm merits further exposition.

Case Report. A 33-year-old woman had severe, debilitating low back pain radiating down both posterior thighs. For 6 months prior to admission, she noted feelings of numbness in her left foot and toes. She denied any bowel, bladder, or sexual dysfunction.

Neurologic examination found left paravertebral spasm in the lumbosacral area with pelvic tilting. Motor power was undiminished for all groups tested in the lower extremities. Sensory testing elicited left S1 hypesthesia. The ankle jerks were depressed bilaterally. Straight-leg raising was markedly restricted on the left side.

A CT scan (Fig. 1) performed as an outpatient procedure was consistent with a herniated disk at the left L5-S1 level. X-rays of the lumbosacral spine showed an area of lucency in the left sacrum with mottled sclerosis in the adjacent iliac bone. Myelographic study (Fig. 2) revealed a block to the caudal flow of contrast media at the L5 level. Because of the radiologic findings in the left iliosacral joint, a malignant epidural tumor was the preoperative diagnosis.

The patient underwent laminectomy at the L5 and S1 levels. The operative findings were vascular neoplasm filling the epidural space, arising from the periosteum of the sacrum, and not invading the dura. A frozen section was reported as fibrofatty tissue with areas of undifferentiated malignant tumor cells. Since the sacral bone appeared to be extensively involved in a malignancy, no further excision was performed beyond gross total removal of the visible epidural mass.

Permanent histologic sections demonstrated uniform tumor cells invading the epidural tissue (Figs. 3, 4). The cells had oval nuclei and small inconspicuous nucleoli (Fig. 5). Periodic acid-Schiff stain showed glycogen-rich granules in the cytoplasm (Fig. 6). The features were interpreted as Ewing's sarcoma.

The patient's initial symptom, pain, resolved. Results of diagnostic studies for metastases, including radioisotope bone scan, skeletal x-ray survey, and lung tomography, were negative except for the left sacroiliac joint and operative site. She became fully ambulatory and was discharged home on the sixth postoperative day.

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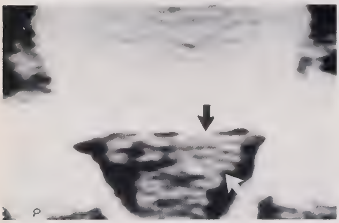


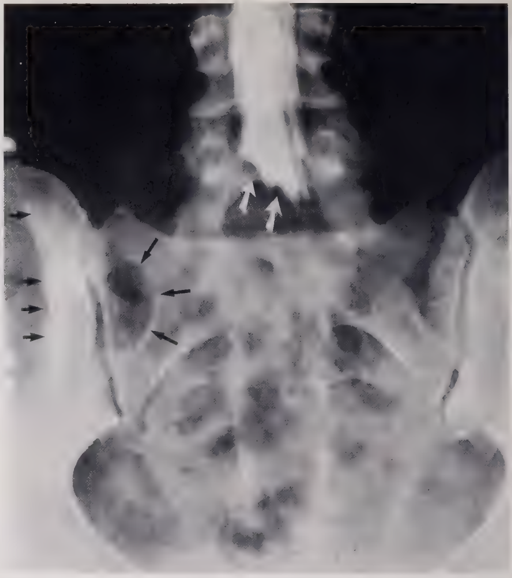
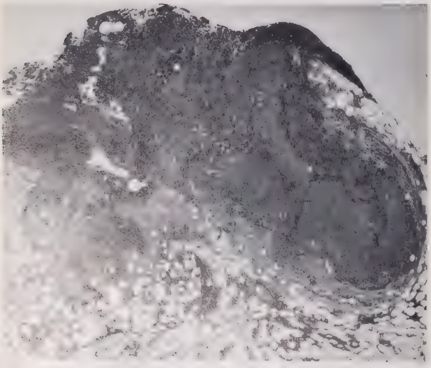


Fig. 1. Left High-definition magnification CT at L5-S1 level, showing left anterolateral extradural lesion simulating disk herniation. **Fig. 2. Right** Lumbar metrizamide myelogram. Observe extradural block at L5 level with typical feathering of caudal sac (white arrows). Note lytic (large black arrows) and sclerotic (small black arrows) changes about left sacroiliac joint.

Outpatient intravenous chemotherapy was instituted: vincristine 1.5 mg/m^2 on days 1 and 22, adriamycin 75 mg/m^2 on day 2, and cyclophosphamide 1400 mg/m^2 on day 23. On day 42, 8 weeks after her initial hospitalization, the patient was readmitted for repeat laminectomy and exploration of the left sacroiliac joint. No residual neoplasm was found in the epidural space or sacrum. Multiple biopsies of the sacroiliac joint produced only benign fibrotendinous tissue with focal chronic inflammation. Chemotherapy was restarted: intravenous vincristine 1.5 mg/m^2 on days 45, 52, and 59, and intravenous adriamycin on day 60. On day 80, the patient returned to the original schedule of vincristine on days 1 and 22, adriamycin on day 2, and cyclophosphamide on



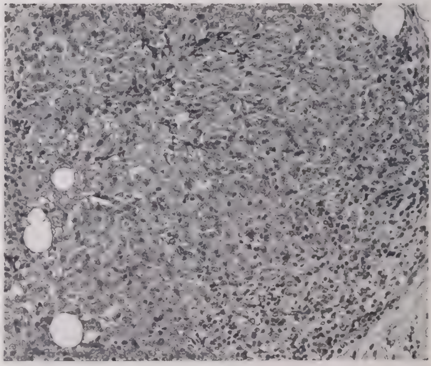


Fig. 3. **Left** Low-power view of broadly infiltrating neoplastic tissue, showing involvement of epidural fat (H & E ×15). **Fig. 4. Right** Uniform, immature, closely packed tumor cells with single oval nuclei, fine nucleoli, and lightly eosinophilic, vacuolated cytoplasm. Note sparse lymphocytic infiltrate (H & E ×156).

TABLE 1
Reported Cases of Primary Epidural Sarcoma

Case	Age	Sex	Site of epidural mass	Therapy	Period of follow up	Result
1	17	M	S1–S2	excision	1 mo	death
2	20	M	T2–T5	excision, radiation, nitrogen mustard, cyclophosphamide	1 yr	lung & bone metastases death
3	18	F	L5	excision, radiation, nitrogen mustard	6 mo	lung & bone metastases death
4	19	M	L2–L3	excision, radiation, adriamycin	2 yr	no recurrence
5	10	M	L4–S2	excision, radiation, adriamycin, vincristine, actinomycin-D, cyclophosphamide	15 mo	GI metastases death
6	33	F	L5–S1	excision, adriamycin, vincristine, cyclophosphamide, actinomycin-D	3 yr	no recurrence

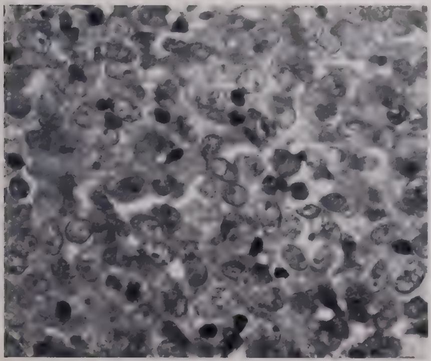
day 23. Four cycles were completed, each over a six-week period.

On day 248, a second regimen of intravenous chemotherapy was begun: vincristine 1.5 mg/m^2 on days 1 and 22, actinomycin-D 0.45 mg/m^2 on day 1, and cyclophosphamide 1400 mg/m^2 on day 23. Seven cycles were completed, each over a six-week period. Follow-up CT and MRI studies over a 3-year period showed no recurrence or metastasis.

Discussion. In a recent study of 140 patients with histologically verified Ewing's sarcoma in every part of the bony skeleton, Wilkins et al (7) recommended that all accessible lesions should undergo surgery and chemotherapy and reserved radiation therapy for cases with incomplete excision. Extraskeletal forms of Ewing's tumor were reviewed by Angervall and Enzinger (4) in 1975; out of 39 neoplams, only 3 cases of primary epidural sarcoma were described. Another instance was reported by Fink and Meriwether (5) in 1979, and one more case by Spaziante et al (6) in 1983.

The data in our own case were somewhat unusual (Table). The patient is only the second woman in a small group of six patients. Her symptoms began in the fourth decade rather than the first two decades of life. She was treated with surgery and chemotherapy and without radiation. Her survival period with no recurrence on follow-up, three years, is the longest recorded; in contrast, four of the other five patients described in the literature died within 15 months of presentation.

Most of the patients had signs and symptoms of disk disease. On the basis of CT alone, the initial impression in our own case was a herniated



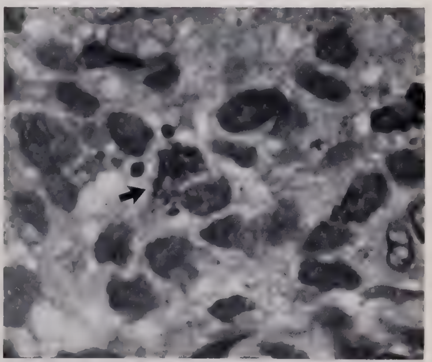


Fig. 5. Left High-power view. Note indistinct cellular margins, thin nuclear membranes, and fine chromatin pattern (H & E ×625). **Fig. 6. Right** Periodic acid-Schiff stain, revealing presence of positive staining granules (arrow) that are rich in glycogen (diastase sensitive) (PAS ×1560).

nucleus pulposus. Myelographic study was crucial in making the diagnosis of an extradural mass lesion. Although nonmetastatic tumors of the spinal epidural space are relatively infrequent, early recognition may result in appropriate specific treatment.

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Megacolon and Volvulus Complicating Progressive Systemic Sclerosis

MARGARET BRANDWEIN, M.D., AND IRA S. SCHWARTZ, M.D.

Abstract

Progressive systemic sclerosis (PSS) is a disease of unknown etiology characterized by connective tissue proliferation and vascular sclerosis in many organ systems. A patient with PSS associated with colonic amotility, megacolon and volvulus necessitating colectomy is presented. The pathologic changes consisted of severe inflammation with dense fibrosis and atrophy of the muscularis propia with replacement by connective tissue in the colonic wall. Although symptomatic colonic involvement in PSS is not common, it may be a source of significant morbidity.

Progressive systemic sclerosis (PSS) is a disease of unknown etiology characterized by connective tissue proliferation within many organ systems associated with a variety of functional disorders. Cutaneous manifestations may dominate the clinical picture; hence the traditional term scleroderma. In a study of 58 autopsy cases, D'Angelo (1) found fibrosis and vascular lesions in the skin (98%), gastrointestinal tract (74%), lungs (59%), kidney (49%), pericardium (41%), and myocardium (26%). More than half of patients with PSS have clinical evidence of gastrointestinal involvement, the esophagus being the most common site of pathologic change. The colon is the least commonly involved gastrointestinal site. Rake (2) is credited with the first description, in 1931, of colonic dilatation and obstruction secondary to PSS, requiring colectomy. Case reports of colonic obstruction, megacolon, volvulus, perforation, and colitis have subsequently appeared; however, PSS remains a relatively rare cause of these colonic complications. The patient reported here developed megacolon, sigmoid volvulus, and intestinal obstruction secondary to PSS.

Case Report. The patient, a 52-year-old white woman with a five-year history of Raynaud's phenomenon, complained of increasingly severe constipation for the same period of time, treated with enemas and multiple medications. She had no dysphagia or evidence of pulmonary insufficiency. Facial telangectasias were present for the past 2 years and recently she had noticed thinning of her lips. One month prior to transfer to The Mount Sinai Medical Center she was admitted to another hospital with the symptoms of large intestinal obstruction, which was unresponsive to conservative measures.

The patient was a thin white woman with absent eyebrows, dry hair, thickened skin over the forehead, and telangectasias over the nose and lips. Her abdomen was mildly distended and soft with decreased bowel sounds; guarding and rebound were absent. Her upper extremities were cold with sclerodactyly, digital infarcts, and telangectasia.

Laboratory values included a total white blood cell count of 4,000/cu.mm, Hbg of 10g/dl, decreased serum total protein of 5.6 mg%, and albumen of 2.9 mg%. Serum antinuclear antibodies

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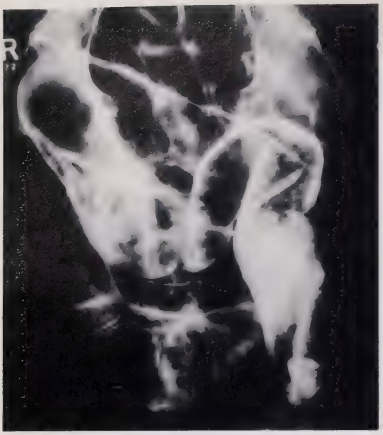


Fig. 1. Air contrast barium enema showing extreme dilatation of colon with loss of haustrations.

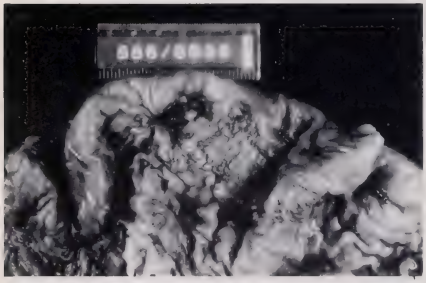


Fig. 2. Resected specimen showing ulceration and chronic inflammation of colonic mucosa.

(ANA) were present at a titer of 1:160 with a nucleolar staining pattern; Scl-70 antibodies were negative. Barium enema performed at the other institution showed a markedly dilated large intestine with loss of haustrations (Fig. 1).

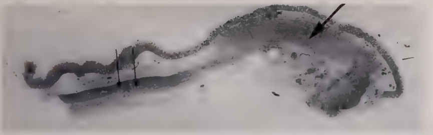
At laparotomy, scattered inflammatory adhesions were present. The colon was massively dilated from the cecum to the sigmoid, where a volvulus was present. The small intestine was noted to be hypotonic. A subtotal colectomy and ileostomy was performed. Postoperatively the patient had crampy abdominal pain thought to be secondary to bacterial overgrowth which responded to tetracycline therapy. She was discharged after 15 days.

Pathological Findings. Examination of the resected colon revealed dilatation with loss of haustration. Two large mucosal ulcerations were present, measuring 13 cm × 1.5 cm and 12.5 cm × 7 cm. The mucosa otherwise had a diffuse granular appearance with small intervening normal areas (Fig. 2). Histologically, severe inflammation with foci of transmural extension, ulceration, and significant fibrosis of the submucosa, lamina propria, and muscularis were noted. The fibrosis extended into areas with an overlying intact mucosa. In some zones, the muscularis was thinned to the point of being entirely replaced by collagen (Figs. 3, 4). Medium-sized arteries showed only minimal intimal thickening; no vasculitis was observed. Pigmented histiocytes in the lamina propria were consistent with melanosis coli. A biopsy of the stomach wall taken at laporotomy revealed fibrosis.

Discussion. The diagnosis of PSS in this woman was based on the long history of Raynaud's phenomenon, subsequent characteristic skin changes, and the serologic finding of positive antinuclear antibodies with a nucleolar staining pattern most often associated with PSS. Approximately 70% of cases of PSS may be negative for antibodies to Scl-70, a labile nuclear protein. This patient's clinical picture was dominated by intractable obstipation with the development of megacolon and volvulus, for which a total colectomy was ultimately necessary.

The colonic histology is typical of that seen in PSS: dense fibrosis throughout the submucosa, lamina propria, and muscularis and atrophy of the muscularis. Ulceration, chronic inflammation with secondary endarteritis obliterans, and spontaneous perforation have also been described (3). Although the latter histologic features may also be seen in inflammatory bowel disease, dense transmural fibrosis and atrophy of the muscularis are not features of ulcerative colitis or Crohn's disease.

The etiology of generalized fibrosis in PSS remains unknown. Some investigators believe the primary event is vascular; others assume that the vascular changes are secondary to fibrosis (4). The characteristic vascular lesion in PSS as described in the skin, lung, and kidney consists of intimal proliferation, medial hypertrophy, and basement membrane thickening. The change described within intestinal wall vessels have varied; intimal proliferation and mucinous degeneration are reported by some observers (5). An intense vasculitis of the mesenteric vessels has been seen (6); in other patients, including the one reported here, no specific vascular lesion can be demonstrated. Telangectasias of the colon have been reported (7, 8) and may be manifested



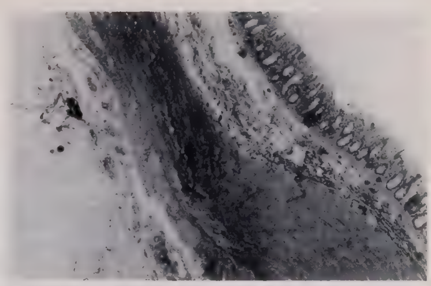


Fig. 3. Left Fibrosis expanding muscularis propria (large arrow) and partially replacing it (small arrows). (Trichrome stain, whole mount). **Fig. 4. Right** Enlarged view (trichrome, 40× original magnification).

clinically as chronic lower gastrointestinal bleeding, although some authors caution that other causes of lower gastrointestinal bleeding must be excluded in patients with PSS. The progressive colonic fibrosis and loss of functional muscularis leads to colonic immotility, sacculation, and dilatation. The increased slackness of the intestine predisposes to volvulus formation. Symptoms may include constipation, sometimes alternating with diarrhea.

The reported colonic complications of PSS include stercoral ulceration with resultant stenosis (9), perforation (10, 11), colitis (12) which may spontaneously perforate (3), megacolon requiring resection (5), sigmoid volvulus (13), traveling volvulus (14), and transverse colon volvulus (15), an otherwise rare entity. Rectal bleeding and diarrhea may lead to an erroneous diagnosis of ulcerative colitis. However, scleroderma colitis is resistant to steroids (16, 17).

Barium enema may provide diagnostic findings for colonic involvement in PSS. Martell (18) reported the loss of colonic haustration, giant sacculations, increase in colonic length, and varying degrees of colonic dilatation. The last two features, when present, serve to differentiate this process from ulcerative colitis. Martell indicates that in none of the 20 cases reported was the colon foreshortened or clearly reduced in caliber, which is characteristic of ulcerative colitis. Wide-mouthed sacculations may also be present with amyloidosis or small infarcts (19).

Acknowledgments

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Lung Function and Health Attitudes and Habits in Professional Wind Musicians and Vocalists

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Abstract

To determine whether the pulmonary function of professional vocalists and wind instrument players is affected by their training, 113 musicians were given pulmonary function tests and questionnaires. Information on respiratory symptoms, perceived susceptibility to and severity of respiratory diseases, and participation in preventive measures was obtained. The control group, 31 string or percussion players, was not significantly different in pulmonary function testing from the 34 vocalists and 48 wind instrumentalists included in the series. The singers, however, exhibited greater health awareness, exercised more, and smoked less than their colleagues. Moreover, these differences in health attitudes and habits were associated with a lower incidence of physician-diagnosed respiratory illness and less absenteeism resulting from respiratory illness among vocalists than among the other musicians. Although pulmonary function itself was, in this study, unaffected by the excessive use of respiratory muscles, the findings may indicate an unexpected lifestyle difference, a selection process, or a protective effect on pulmonary function of the training of singers.

Ten million Americans are afflicted with emphysema, chronic bronchitis, and asthma (1). Wind and brass musicians and vocalists may be predisposed to these diseases owing to the chronic use of their respiratory muscles in the performance of their occupations (2, 3). Occupational lung disease has implications for disease screening and preventive measures as well as for health and disability insurance provisions. Yet these groups may, by virtue of their training or their health attitudes and health habits, possess improved lung capacities and lung function (4–7). This information could be useful to chronic obstructive lung disease (COPD) patients, who might benefit from engaging in similar activities, or to healthy individuals, who might use these measures preventively.

Studies of lung function in these muscians have shown conflicting results ranging from reduction in function (2, 3) to no difference (8–11) to improvement (4–7) in function. Practically all of these studies suffer from the use of published normal standards as controls. Several of these studies of "normal" populations can be faulted for their use of hospitalized patients (12) and are difficult to compare because of variations in technique, equipment, and environment as well (12–18). Studies of musicians have been deficient because of differences in testing methods and equipment from the control studies used, use of nonmusician controls (3), few women subjects, small sample sizes (7), anecdotal references to data (2, 9), lack of control for confounding factors (4, 6) such as smoking (3, 4), inclusion of players of limited or amateur experience (4, 6), other forms of selection bias (5, 10), and omission of a supplemental questionnaire.

Ventilatory muscle training similar to that of singers and wind musicians has recently been suggested to exert a beneficial effect on exercise tolerance, on physical fitness (19–21), and occa-

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sionally on pulmonary function (22) in COPD. Improved pulmonary function in musicians would support this form of therapy in patients.

This article reports a study of health attitudes, health habits, and respiratory function among 113 professional New York City musicians. Data on 34 vocalists and 48 wind musicians (woodwind and brass) were analyzed and compared with data obtained from 31 control musicians with the objective of determining whether pulmonary function is better in vocalists and wind musicians than in controls working under similar environmental conditons. If so, is the improvement secondary to training and occupation? Or are differences in lung function (by objective and subjective clinical and historical criteria) related to health beliefs and behaviors?

Methods

Protocol. One hundred thirteen professional musicians ranging from 25 to 80 years of age voluntarily participated in this study. "Professional musician" was defined as a highly trained performer currently and regularly employed in a performing role. Included in this study were singers from the New York City Opera and Choristers' Union (AGMA) and wind and string or percussion instrument players from the American Ballet Theatre, Guggenheim Concert Band, Broadway plays, and "club daters" who generally perfom at wedding receptions and similar affairs. Testing was performed at union halls or the subjects' place of rehearsal or performance.

Questionnaire. Prior to testing, all subjects completed a self-administered questionnaire similar to Ferris' in the Epidemiology Standardization Project (23), which covered performance; respiratory, smoking, and occupational histories; complete medical history; and additional questions designed by the author on health attitudes and habits.

No individual was refused participation on the basis of an existing medical problem unless it interfered with completion of the tests. Excluded from the study were seven musicians who both sing and play a wind instrument.

For purposes of this study, a current smoker was defined as "regular" cigarette, cigar, or pipe smoker up to a month prior to testing. A nonsmoker was either an ex-smoker (ceased smoking more than one month ago) or had smoked less than one cigarette per day in one year, one cigar per week in one year, less than 20 packs of cigarettes, or less than 12 oz tobacco in a lifetime (23, 24).

Equipment and Quality Control. A portable Collins' "Eagle" (7-liter) water-sealed spirometer was used to obtain MVV, FEV_1, FVC, $FEF_{25-75\%}$, $FEV_1/FVC\%$ with daily calibration checks using a 3-liter syringe.

Analysis. The best of at least two MVV tests, reproducible to within 5%, was accepted (12, 14, 25, 26). Spirometry was repeated at least three times or until duplicate values were obtained that agreed within 5%, and the best reproducible values of FEV% predicted and FVC% predicted were used in the analysis (12, 14, 25, 26). The $FEF_{25-75\%}$ accepted was obtained from the single test with the greatest sum of FEV_1 and FVC. Twenty-five musicians were excluded on the basis of FEV_1 or FVC% predicted values that were not reproducible to within 5% (23, 25) on repeated testing. Pulmonary function test values were expressed as a percentage of the predicted values. The predicted values of Morris et al were used (13), with values adjusted for black subjects by subtracting 13% from the normal predicted values for white subjects (25). An "abnormal" subject was defined as having an FEV_1 or FVC% predicted <75%, and $FEV_1/FVC\% < 70\%$ (25).

Statistical methods included Student's *t* tests for continuous variables, χ^2 tests or Fishers's exact two-tailed tests (for smaller sample sizes) for discrete variables, and general linear models procedure using variables that differed significantly ($p < 0.05$) between groups in the previous analyses.

Factors considered important were independent variables such as sex, height, age, weight, years performing, cough, sputum, wheezing, smoking status, occupational history, and exercise; and dependent variables such as MVV, FVC, FEV_1, $FEV_1/FVC\%$, and $FEF_{25-75\%}$. The number of subjects complaining of symptomatic wheezing did not differ significantly between groups in preliminary descriptive analyses; this variable was not included in the multiple regression analysis. The variable regular exercise was similarly excluded. Occupational history was also dropped from consideration because so few participants had any relevant exposure.

Multiple regressions using a general linear models procedure allowed a direct estimate of the difference between groups while adjusting for the effect of confounding variables. Included in the model were weight, cough, sputum, smoking status, and years performing. These variables were analyzed independently with respect to the PFT's and then were analyzed successively with all but one held constant, thereby eliminating variation resulting from these variables.

TABLE 1

*Comparison of Pulmonary Function Variables in 113 Musicians**

Variable	String/percussionists (n = 31)		Wind/brass (n = 48)		Vocalists (n = 34)	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Age (years)*	31	43.5 ± 13.9	48	47.4 ± 14.5†	34	41.3 ± 11.2†
Years performing*	30	22.5 ± 11.2	47	27.5 ± 14.7‡	34	18.6 ± 11.8‡
Height (in.)*	31	68.7 ± 3.4	48	69.2 ± 2.9	34	68.7 ± 3.4
Weight (lb)*	31	157.4 ± 26.6†	48	170.0 ± 26.0†	34	165.6 ± 26.1
Sex§						
Male	25 (81%)		43 (90%)		26 (76%)	
Female	6 (19%)		5 (10%)		8 (34%)	
Race§						
White	31 (100%)		45 (94%)		34 (100%)	
Black	—		3 (6%)		—	

* p values were obtained by Student's t test. p values < 0.05 were considered significant.

† $p < 0.05$.

‡ $p < 0.01$.

§ p values were obtained by χ^2 test or Fisher's exact two-tailed test if over 20% of cells contained less than five subjects.

Results

One hundred and thirteen professional musicians were included in this study. Controls were 31 string or percussion players. Forty-eight musicians were wind instrument players, and 34 were singers.

Population Characteristics. The average age (Table 1) of wind instrument players, 47 years, was significantly greater ($p < 0.05$) than that of the singers (41 years) and not significantly greater than that of the controls (44 years). The wind group, which consisted largely of older club daters, had more performing experience than the control group (28 versus 23 years) and significantly more experience than the singers (19 years). The average of all was 23 years' experience. Because these differences in performance history might affect the study results, years performing was controlled for in later multiple-regression analyses. Height was similar in all three groups, but weight was significantly greater in the wind group (170 lb) compared with the control group (157 lb). There were 94 men (25 controls, 43 wind players, 26 vocalists) and 19 women (6 controls, 5 wind players, 8 vocalists). Although the wind players tested were primarily male (only 10% were females), there were many females [illegible] among the singers. All of the controls and singers were white. Three of the 48 wind players were black.

Pulmonary Function. No significant difference was found between groups in any of the pulmonary function variables tested (Table 2). Four musicians were considered abnormal by standard spirometric criteria. Three of the four played string or percussion instruments and were either current or ex-smokers over the age of 55. The fourth was a 31-year-old nonsmoking brass instrument player with pectus excavatum.

Two primary symptoms in the diagnosis of lung disease are cough and sputum (Table 3); both reported significantly less often by wind players than by controls (cough: 4% versus 19%; sputum: 27% versus 48%). However, more wind players (31%) than vocalists (21%) and controls (19%) stated that they visited their physician for a breathing problem. In addition, more wind players (29%) than vocalists (18%) and controls (16%) were told by their physician that they suffered from a chest illness. More wind players (9%) than vocalists (6%) and controls (3%) were taking bronchodilators to alleviate a respiratory condition. In the past three years, wind players missed more work days (3.25) than vocalists (1.29) and controls (0.78). Yet, when asked if a respiratory problem ever kept them out of work, more vocalists (18%) than wind players (10%) and controls (6%) responded "yes."

The three occupational exposures most often cited were asbestos, shipyards, construction/insulation/demolition/plumbing. These findings were not statistically significant. Vocalists tended to exercise more (65%) than the wind players (56%) and the controls (52%) and tended to smoke less (12%) than these groups (wind: 29% smokers; controls: 26% smokers).

Health Attitudes. Significantly more singers (88%) than both controls (67%) and wind players (70%) believed that "keeping fit" was important

TABLE 2
*Comparison of Pulmonary Function Variables in 113 Musicians**

	String/percussionists ($n = 31$)		Wind/brass ($n = 48$)		Vocalists ($n = 34$)	
Variable	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
MVV % predicted	31	112.5 ± 25.2	48	118.2 ± 22.2	34	118.5 ± 18.2
FEV_1 % predicted	31	101.9 ± 17.6	48	103.5 ± 15.5	34	106.5 ± 3.4
FVC % predicted	31	97.2 ± 13.8	48	98.7 ± 13.1	34	102.8 ± 11.7
FEV_1/FVC%	31	79.1 ± 9.4	48	78.0 ± 6.8	34	79.4 ± 7.6
$FEF_{25-75\%}$	31	93.2 ± 34.2	48	90.3 ± 30.6	34	92.9 ± 28.1

All pulmonary functions (except FEV_1/FVC%) are expressed as the percentage of Morris' predicted value according to age, sex, and height. MVV, maximum voluntary ventilation; FEV_1, forced expiratory volume after 1 sec; FVC, forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow at 25–75% of vital capacity. p values were obtained by Student's t test. p values < 0.05 were considered significant.

to being able to perform up to their own standards. Singers also considered themselves to be significantly (74%) more suceptible to illness than wind players (47%) and somewhat more susceptible than controls (60%).

Eighty-two percent of singers cited respiratory conditions as a major illness or risk of their occupation (versus wind 13%, control 7%), 75% of wind musicians cited stress and nervous conditions, and 79% of controls cited muscle "aches and strains." Other occupationally related illnesses or risks mentioned were alcohol and drug abuse, heart and lung disease, hearing loss, lack of exercise, foul air, and dental problems. Vocalists stated that significantly larger numbers of their group than wind players (72% versus 43%) were affected by the risk most often cited for their group. Ninety percent of singers believed that prevention of the occupational risk cited was possible, as opposed to 85% and 83% among the wind players and controls, respectively.

More vocalists (67%) than wind players (47%) and controls (41%) actually participated in preventive health measures, and the "barriers" most often cited were laziness and lack of time in all groups. In addition, management played a role in guiding health behaviors: significantly more vocalists (82%) than controls (56%) stated that smoking was prohibited at rehearsals (winds: 69%).

Multivariate Analysis. To further examine whether instrumental grouping had any independent effect on the parameters studied, the potentially confounding variables such as weight, cough, sputum, smoking, and years performing were controlled for by multivariate analysis. String/percussionists were compared with wind players and with vocalists with and without holding confounding factors constant, and in no case was there any significant difference between them in any of the pulmonary function tests administered.

Although there was little difference between groups, one variable in the model did consistently influence the pulmonary function tests in all groups: smoking was, as expected (24), significantly associated with a decrease in all the spirometric results. Other parameters, such as symptoms of cough or sputum or increasing years of performing, did not consistently influence the spirometric variable.

Discussion

The findings revealed an unexpected lifestyle difference, a selection process or survivor bias, or a protective effect of the training of singers on respiratory fitness.

Lack of statistically significant differences in PFTs between groups can suggest several other interpretations: (a) there is no risk or benefit to being trained as a wind player or vocalist; or perhaps (b) training does improve pulmonary function in wind players but not singers (using the reduction in the clinical symptoms of cough and sputum among wind players as evidence for this), but this benefit is offset by the prevalence of smokers in this group; or (c) training does improve pulmonary function in wind players and singers, but not enough for improvements to be detected by PFTs; or finally (d) good habits in vocalists may offset or mask possible detrimental effects of training, but again this is not reflected by the results among wind players, who presumably train similarly.

These interpretations are problematic, though, because differences in PFTs were also not found with confounders eliminated. Also, un-

TABLE 3

Clinical and Historical Features of Respiratory Illness and Health Behaviors in 113 Musicians

	String/percussion (n = 31)				Wind (n = 48)				Vocalists (n = 34)			
	Yes		No		Yes		No		Yes		No	
Variable	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cough*	6	(19)[a]	25	(81)	2	(4)[a]	46	(96)	3	(9)	31	(91)
Sputum*	15	(48)[b]	16	(51)	13	(27)[b]	35	(73)	12	(35)	22	(65)
Visited physician for chest illness*	6	(19)	25	(81)	15	(31)	33	(69)	7	(21)	27	(79)
Physician diagnosed chest illness*	5	(16)	26	(84)	14	(29)	34	(71)	6	(18)	28	(82)
Bronchodilator use*	1	(3)	30	(97)	4	(9)[c]	43	(91)	2	(6)	32	(94)
Average no. days missed work in past three years†	0.78				3.25				1.29			
Time lost professionally due to chest illness*	2	(6)	29	(94)	5	(10)	43	(90)	6	(18)	28	(82)
Occupational exposure‡	3	(10)	28	(90)	8	(17)	40	(83)	3	(12)	31	(88)
Exercise*	16	(52)	15	(48)	25	(56)[d]	20	(44)	22	(65)	12	(35)
Current smoker*[e]	8	(34)	23	(66)	14	(29)	34	(71)	4	(12)	30	(88)

* Values obtained by χ^2 test or Fisher's exact two-tailed test if over 20% of cells contained less than five subjects. p values < 0.05 were considered significant.

† Values obtained by Student's t test.

‡ Exposure to asbestos, shipyards, construction/demolition/plumbing/insulation for < three months.

[a] $p < 0.01$, Fisher's exact.

[b] $p < 0.05$, $\chi^2 = 3.74$.

[c] One subject did not answer question.

[d] Three subjects did not answer question.

[e] Definition of "current smoker" given in text (23, 24).

explored training differences between singers and wind players may explain discrepancies in results between these two groups.

The fact that three of four abnormals were controls, although too small a number to be statistically significant, may indicate decreased function among string/percussionists as a group. However, it is more likely that their particularly reduced PFTs were due to their long smoking histories (24).

Although cough and sputum are less prevalent among wind players (a surprising factor because this group tended to smoke more than the other groups), wind players tended to have more evidence of physician-diagnosed respiratory illness, supported by increased bronchodilator use, time lost professionally owing to chest illness, visits to physician for chest illness, and actual diagnoses of respiratory illness. However, since the PFT and clinical symptom results do not correspond to increased chest illness, diagnosis of these illnesses by the physician may have been made by some other criteria, perhaps abnormal findings on physical examination or an abnormal chest X-ray. Higher prevalence of respiratory illness among wind players than singers may again be due to training differences between these two groups (this question was not addressed by this study) or to the possibility that physicians of wind players are more attuned to respiratory hazards of this profession than those of singers. These physicians might be more likely to screen for and treat these illnesses, whereas vocalists' physicians may tend to dismiss respiratory ailments in their patients as aggravated "hoarse throats" and treat symptomatically only.

Reasons for increased physician-diagnosed illness among wind players might be (a) smoking, (b) little exercise, (c) increased occupational exposures, (d) stress and nervous conditions, many of which may be related to the characteristics of this cohort population. Wind players sampled were, on average, older male club daters who were more likely to have been exposed to asbestos during World War II. They probably smoked more than their younger colleagues because of less knowledge about the risks of smoking and the increased popularity of the habit when they began smoking. In addition, club daters tend to perform in smoke-filled rooms, which may encourage smoking as well.

Perhaps because their "instrument" is more threatened than other musicians' when afflicted by an upper respiratory infection, singers perceive (though they do not appear to actually have) a greater susceptibility to respiratory disease. They tend to engage more frequently than their colleagues in preventive measures such as exercise and abstention from smoking. This may account for their lower rates of physician-diagnosed respiratory problems. Part of this health-conscious attitude may also stem from the fact that the singers sampled tended to be younger than the wind players. This age cohort, in the general population, is more aware of health risks and the importance of "keeping fit" and of taking preventive measures. Despite these differences in habits and perceptions, no effect on PFTs was noted.

The PFT results confirm those of Heller et al (8), Luongo (9), Navrátil and Rejsek (10), and Borgia et al (11). However, there are differences in testing methods, sample size, and choice of controls. Testing methods in this study were performed according to stringent American Thoracic Society (26) and Epidemiology Standardization Project (23) criteria; sample size was usually large enough to be statistically useful; predicted values were those of Morris et al (13), whose normals were nonsmokers; and most important, controls chosen for this study were musicians who were presumably subject to the same environmental exposures and training schedules during the performance of their jobs as the experimental group. In addition, few of the investigators used a questionnaire (5, 10), and none used this method to determine the relationship of PFTs to health attitudes and behaviors.

The results contradicted those of Singer (2) and Akgün and Ozgönul (3), who reported emphysematous changes and increased respiratory disease among singers and wind players. Singer's discussion was anecdotal and was unsupported by a scientifically controlled study. Akgun's study was complicated by uncontrolled confounding factors, such as smoking, exclusion of women, and no musician controls.

The PFT results also contradicted those of Bouhuys (4), Stauffer (5), Tucker et al (6), and Gould and Okamura (7), who found improved lung volumes and more efficient mobilization of lung capacity among singers and musicians. These studies too were flawed by small sample sizes, few or no women, nonmusician controls, players of insufficient experience, use of poorly chosen predicted normals, lack of controls for smoking, and use of a subject population preselected for superior physical fitness.

It is unclear whether the PFT results could be extrapolated to explain the lack of improvements in PFTs of patients with COPD who undergo ventilatory training (11, 19–21). But though PFTs were not improved by training in normal musician subjects or in COPD patients, perhaps exercise tolerance, general "well-being," and ability to better perform the "activities of daily life" as determined by the subjective criteria discussed above are improved by training and good health habits (as suggested by this study)—reason enough to adhere to them.

As evidenced by the large number of vocalists who wrote that smoking was prohibited at rehearsals, management may in this case recognize the importance of regulating health habits to keep employees fit. Workers should be encouraged with financial and other incentives by their employers, unions, and health insurance companies to stop smoking or at least to refrain from smoking in the workplace and to participate in preventive health measures such as diet, exercise, and physical fitness programs as well as in respiratory disease screening examinations.

General recommendations for the physician include education of the patient in the risks for pulmonary disease and in the use of preventive measures, and screening for respiratory disease using smoking history rather than occupational history as a factor predictive of respiratory illness.

Research should be directed toward further assessment of risk or benefit factors for respiratory disease and toward development of additional sensitive screening tests.

Summary

The commonly held assumption that vocalists and wind players are physiologically superior to other musicians with respect to their pulmonary function (PFT's) was not supported by this investigation. Neither was it confirmed that wind musicians and vocalists suffer from occupationally induced respiratory disease. Indeed, no significant difference in PFT's between groups was noted, even when confounding factors were eliminated. However, differences were found between groups in the clinical criteria of lung disease and health habits as assessed by the questionnaire. Wind players suffered less from cough and sputum than both singers and controls, for unknown reasons. Yet they were more susceptible to respiratory illness and less likely to engage in preventive health measures than singers. The better health attitudes and habits of singers

may have fueled the assumption of better lung function among them and may account for their greater respiratory fitness. Assessment of causality between training or health habits and pulmonary function was not possible from this study.

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Student Corner

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Ocular Manifestations of Crohn's Disease: Literature Review

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Crohn's disease (granulomatous ileocolitis) is a systemic illness with multiple extraintestinal complications. Since 1925, when Burrill Crohn first described keratoconjunctivitis, iritis, and xerophthalmia in two patients with ulcerative colitis (1), eye lesions have been found in a small but significant number of patients with inflammatory bowel disease. This paper discusses the ocular manifestations associated with Crohn's disease, theories of their pathogenesis, patterns, and treatment.

Manifestations

Symptomatic eye disease is present in 2%–6% of patients with Crohn's disease (2–5). However, the true incidence of the ocular manifestations is difficult to determine. One problem is deciding which eye lesions are directly attributable to the disease and which are simply random associations that can be found in the general population with similar frequencies. A second problem is that the few retrospective studies available are based on a small number of patients who sought treatment for ocular complaints. These studies do not account for asymptomatic yet characteristic changes resulting from Crohn's disease. Asymptomatic manifestations are rarely screened and thus are not generally included in studies on the incidence of ocular manifestations of Crohn's disease.

Virtually every type of eye pathology has been reported in patients with Crohn's disease. These reports range from benign occult changes to diseases that can cause irreversible blindness: uveitis, episcleritis, blepharitis, cataracts, central serous retinopathy, conjunctivitis, corneal ulcers, disc edema, keratopathy, macular hemorrhage, neuroretinitis, orbital cellulitis and myositis, proptosis, retinal vascular disease, retrobulbar neuritis, scleritis, scleromalacia, and xerophthalmia (1–19).

Edwards and Truelove (6) were the first to find a significant incidence of ocular manifestations in a survey of patients with ulcerative colitis. Conjuctivitis and iritis were the most common eye lesions in their series. Korelitz and Coles (2) wrote the landmark article describing the association between inflammatory bowel disease and uveitis. Two percent of the patients they surveyed had at least one episode of uveitis. The study by Hopkins et al (4) found uveitis to be the most common eye abnormality in patients with Crohn's disease. A 1984 study by Knox et al (7) determined that uveitis was among the two most common eye complications, the other being episcleritis.

The iris, ciliary body, and choroid comprise the uveal tract; uveitis is an inflammation involving one or more of these structures. The most common form associated with Crohn's disease is anterior uveitis or iridocyclitis. The patient's typical initial symptoms are pain, photophobia, lacrimation, and blurred vision of sudden onset. The clinical signs are circumcorneal injection of the episcleral vessels; contraction of the pupil; an anterior chamber exudate detectable on slit-lamp examination by the presence of inflammatory cells floating in the aqueous humor; and translucence of the aqueous (flare) due to an increased concentration of albumin. Usually the inflammation does not last more than a few weeks. If, however, the inflammation persists, uveal tract adhesions (synechiae) form. Anterior synechiae between the ciliary body and cornea cause obliteration of the pupil aperture and loss of ac-

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commodation. This inhibits the drainage of aqueous humor through the canal of Schlemm, and hence secondary glaucoma results. Posterior synechiae forming between the iris and the lens lead to cataract formation. Anterior uveitis may also spread to the choroid, causing posterior uveitis and blindness.

Uveitis may have a spectrum of initial symptoms. Wright et al (8) found that 11.8% of ulcerative colitis patients harbored evidence of either past or present asymptomatic uveitis as compared with 2% in a control group. Another study (9) examined 26 children with inflammatory bowel disease. Six (32%) of the 19 Crohn's disease patients examined had evidence of asymptomatic uveitis, whereas none of the children with ulcerative colitis did. The uveitis in these children was found to be transient and cleared within one year. Both studies required the presence of inflammatory exudate and aqueous flare in the anterior chamber to make the diagnosis. Inflammatory exudate is the more reliable of these two signs (10).

Episcleritis frequently appears in association with Crohn's disease. The usual symptom is a raised nodule resulting from a localized area of hyperemia in the episcleral tissue that causes mild discomfort. In a series of 47 patients reported by Knox et al (7), 8 (17%) experienced this benign inflammation of the outer layers of the anterior sclera. Another study (4) reported episcleritis in 2 of 21 patients with ocular disease and granulomatous ileocolitis.

Wright (11) described three patterns of conjunctivitis that he found in 5 patients with inflammatory bowel disease: granuloma formation, fibrovascular membrane proliferation, and pyoblepharoconjunctivitis.

Distinctive benign corneal infiltrates, as well as corneal ulcers, have been reported in Crohn's disease. Schulman and Sugar (12) described small, oval, white peripheral corneal infiltrates in 3 patients with inflammatory bowel disease. These infiltrates produced no complaints. Knox, Snip, and Stark (13) examined 3 patients with both small, rounded elevations of the corneal epithelium and subepithelial infiltrates located 2–3 mm inside the entire corneoscleral limbus. The lesions were so unique that these ophthalmologists referred a fourth patient with this keratopathy for subsequent workup. Extensive radiographic evidence of Crohn's disease was discovered even though the patient was asymptomatic at the time.

Cataract formation in Crohn's disease has two etiologies. Either long-term steroid therapy or recurrent uveitis may induce posterior subcapsular cataracts. However, as with many other ocular manifestations, its prevalence in the general population makes assessing the increased risk of cataract formation difficult in the patient with Crohn's disease.

In 1984, Knox, Schachat, and Mustonen (7) classified the ocular manifestations into three categories—primary, secondary, and coincidental. On the basis of their experience with 47 patients over a 20-year period, they defined primary ocular complications as those which occur frequently in Crohn's disease and which tend to correspond with the activity of the bowel disease. The manifestations that fall into this category are uveitis, episcleritis, corneal infiltrates, scleritis, macular edema, central serous retinopathy, and proptosis. Knox further theorized that these primary complications resulted in secondary complications. Examples of secondary complications include cataracts, induced by uveitis or steroids; and decreased tear formation, presumably caused by malabsorption of vitamin A. Coincidental complications—conjunctivitis and corneal ulcers are two examples—occur frequently in the general population and cannot be attributed to Crohn's disease on the basis of available studies. Coles (7), in his review of the Knox paper, criticized this differentiation. Coles believes scleromalacia, retinal detachment, disc edema, decreased tear formation, and cataracts are all primary manifestations of Crohn's disease. He concluded that the Knox classification was unnecessarily complicated.

It would be useful to have a classification system differentiating ocular manifestations attributable to Crohn's disease from coincidental eye diseases. However, at this point we do not have the knowledge to make such a differentiation. The ability to distinguish between the forms of eye disease awaits discovery of the pathogenesis of the extraintestinal manifestations of Crohn's disease.

Etiology and Pathogenesis

The etiology of the extraintestinal manifestations of Crohn's disease is unknown. Crohn himself considered vitamin deficiency to be the cause of the eye symptoms in the patients he reported (1). The prevailing theory, however, is that circulating immune complexes in patients with Crohn's disease account for the ocular syndromes. Disruption of the mucosal barrier may allow bacterial pathogens present in the colon to enter the circulatory system, providing an antigen source. When the resulting antigen-antibody complexes are deposited, they provoke inflammatory responses that result in tissue damage. These responses are mediated primarily by the complement system.

The possible association between HLA B27 and ocular manifestations of Crohn's disease is a key area of research that requires exploration. The haplotype HLA B27 is found with increased frequency in patients who have acute anterior uveitis. Patients with Crohn's disease and ankylosing spondylitis have a very high frequency (75%–90%) of HLA B27 (14). Coupling this with the data available on asymptomatic manifestations gives rise to the speculation that a large population with occult systemic changes exists in Crohn's disease. Only genetically or immunologically susceptible individuals may actually develop symptoms.

Patterns of the Eye Disease

The onset of the ocular manifestations is unrelated to the onset of the gastrointestinal symptoms. As would be expected, most cases of associated eye disease are discovered after the diagnosis of Crohn's disease has been made. However, Korelitz and Coles (2) reported that in 3 of the 4 patients with granulomatous ileocolitis in their study, uveitis occurred prior to the onset of the gastrointestinal disease. In one patient, uveitis preceded the diagnosis of Crohn's disease by 20 years. Another example is provided by Petrelli et al (15), who reported two patients with peripheral corneal ulcers, episcleritis, and scleritis just prior to the onset of symptomatic Crohn's disease. Finally, a major study (4) did not find any relationship between the onset of ocular symptoms and the duration of the disease.

The relationship between the activity of the disease and the ocular complications is less straightforward. Uveitis occurred during periods of active bowel disease and remission with equal frequency in the cases studied by Korelitz and Coles (2). However when Hopkins et al (4) totaled the other ocular manifestations along with uveitis, a different picture emerged. They recorded a 4% incidence rate for ocular complaints during years in which the bowel disease was active, whereas patients in remission for a one-year period had an incidence rate of only 0.2%.

There is significant potential for serious visual impairment. Ten of the thirteen patients in Korelitz and Coles' study had two or more episodes of uveitis. Two suffered blindness. In another series of 21 patients (4), two incurred severe loss of vision.

Greenstein, Janowitz, and Sachar (3) found that the incidence of eye manifestations (as well as joint, skin, and mouth complications) was higher in patients with granulomatous colitis (13%) than in ileocolitis (4%) or regional enteritis (1%). The National Cooperative Crohn's Disease Study (5) reported a 7% incidence of uveitis in Crohn's colitis as compared to a 3.5% overall incidence in Crohn's patients. Hopkins et al (4), however, found no statistically significant difference in the site of the gastrointestinal disease. They reached this erroneous conclusion because they failed to look at the incidence of ocular manifestations of Crohn's disease in the population surveyed. They limited their inspection to the 21 patients with eye disease, failing to account for the fact that Crohn's disease involving only the colon occurs with considerably lower frequency than ileocolitis or enteritis.

Greenstein et al (3) found a similar rate of eye complications in Crohn's disease and ulcerative colitis. However, there is a higher incidence of eye disease in patients with granulomatous colitis (13%) than in those with ulcerative colitis (4%).

Ocular complications are highly correlated with other extraintestinal manifestations of Crohn's disease. Wright et al (8) were the first to note a strong association between uveitis and sacroileitis in ulcerative colitis. In the Korelitz and Coles (2) study, 11 of 13 patients (84%) with uveitis also had some form of arthritis. Hopkins et al (4) found associated joint disease in 43% of their patients with ocular manifestations. Skin manifestations are also found in a high proportion of Crohn's patients with eye disease. Erythema nodosum was noted in 5 of 13 patients (38%) in the Korelitz study, whereas eye and skin manifestations were conjointly present in 14% of the patients in the series of Hopkins et al.

Evidence indicates a higher incidence of ocular manifestations of inflammatory bowel disease in women than in men. Korelitz and Coles (2) reported a 2:1 ratio of female to male patients having such manifestations. Wright et al (8) found a similar ratio. However, in a study confined to Crohn's disease patients, Hopkins et al (4) did not find a statistically significant difference in the male-to-female ratio.

Treatment

Eye lesions associated with Crohn's disease usually resolve with treatment. Anterior uveitis is treated with mydriatics and topical steroids. Topical and oral steroid therapy is used in most of the other eye diseases as well. Symptoms such as night blindness and dry eyes are suggestive of vitamin A deficiency and can be corrected with oral vitamin therapy. In addition, Macoul (16) recommends multivitamin therapy as an adjunct to steroids in the treatment of corneal ulcers.

For the patient who suffers from intractable eye disease, the question of whether to perform elective bowel surgery arises. Four of the patients in the Korelitz and Coles (2) series had colon surgery. Three had no recurrence of uveitis after surgery, and in the fourth patient, the uveitis was milder. Nineteen patients in the study by Hopkins et al had surgery. Of the 4 patients who continued to have complications, 2 had recurrent uveitis, 1 had cataract formation, and another had a unilateral macular hemorrhage. Such data indicate that ocular manifestations of Crohn's disease are usually, but not universally, ameliorated by surgery. The presence of ocular manifestations should support other indications for surgery, but, based on our current knowledge, severe eye complications in patients with Crohn's disease are not clear indications for surgery.

Summary

Approximately 4% of patients with Crohn's disease have symptomatic ocular complications. Studies indicate that a larger, but as yet undetermined, proportion have asymptomatic manifestations. These asymptomatic ocular manifestations may prove to be significant, first, in understanding the pathogenesis of extraintestinal manifestations of Crohn's disease; second, as a possible diagnostic aid in early detection of the disease; and third, as precursors of symptomatic eye disease.

The prevailing theory of Crohn's disease attributes the extraintestinal manifestations to circulating immune complexes. Ocular manifestations may occur at any time during the course of Crohn's disease, even prior to the onset of gastrointestinal symptoms. However, ocular manifestations are more likely to occur when the colon is involved. Eye manifestations are often found in patients who have other extraintestinal manifestations. Although the eye diseases usually respond to therapy, there is significant potential for serious visual impairment.

In light of this information, all patients with Crohn's disease should have routine ophthalmologic examinations. Conversely, Crohn's disease should be considered in the differential diagnosis of patients with anterior uveitis or distinctive corneal infiltrates.

Acknowledgments

I gratefully acknowledge the assistance of Dr. Adrian Greenstein in reviewing this paper. I also extend special thanks to my wife, Mindy Frankel Strauss.

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A Laboratory Preparation Mimicking Human Peptic Ulceration:

A Chronic Antral Peptic Ulcer Postsection and Reanastomosis at the Antral-Fundic Junction in the Rat

Osvaldo M. Tiscornia, M.D., J. De Paula, David Celener, M.D., E. Schiffrin, M.D., O. Nakasato, M.D., Miguel A. Cresta, M.D., H. Waisman M.D., L. Bustos-Fernandez, M.D., and David A. Dreiling, M.D.

In a recent experiment evaluating the trophic effects on rat pancreas induced by various surgical operations on the upper gastrointestinal tract (1), transection and reanastomosis of the anterior and posterior wall of the stomach at the antral-fundic junction (SRAF) was followed, unexpectedly, by chronic peptic ulcerations on either one or both walls of the antrum. Perusal of the literature indicated that human chronic peptic ulceration has never been observed in any animal model. All of the animal protocols attempting to mimic human peptic ulcers so far reported have in fact been simple erosions in the gastric fundus, that is, circumscribed mucosal lesions above the muscularis mucosae, generally restricted to the fundic area.

The purpose of this paper is to report the incidence of chronic peptic ulceration following SRAF and to consider the implications of this experimental lesion on the physiopathogenesis of human peptic ulcer diathesis.

Materials and Methods

Ninety-eight adult Wistar rats were used.

Control Group. Forty-three animals were studied. Their body weight was 491 ± 8 gm. Paired with the different experimental subseries, they were sacrificed within two time periods ranging from 122 to 225 days.

Experimental Groups. Six subseries were investigated.

Group 1. In 25 animals, body weight 477 ± 14 gm, both the anterior and posterior gastric walls were cut through and reanastomosed at the level of the antral-fundic junction (SRAF). The lesser curvature nerves were deliberately sectioned in order to induce antral denervation. The reanastomosis of both the anterior and posterior sides of the stomach was performed by means of interrupted stitches with atraumatic needle and silk 6-0. Pyloroplasty was omitted. The period of observation was 139 ± 11 days.

Group 2. In 8 animals, body weight 515 ± 29 gm, the procedure was identical except that a pyloroplasty was performed concurrently. These animals were observed for 183 ± 3 days.

Group 3. In 8 animals, body weight 478 ± 11 gm, the SRAF procedure was performed but as for cutting of the lesser curvature nerves was avoided by using a dissecting microscope. As in the subseries (1), pyloroplasty was omitted. The animals were sacrificed after 221 ± 1 days.

Group 4. In 5 animals, body weight 481 ± 19 gm, the procedure was SRAF of only the gastric posterior side was performed, i.e. hemisection. The lesser curvature nerves were left intact, as was the pylorus. The rats were studied for 222 ± 2 days.

Group 5. In 4 animals, body weight 481 ± 19 gm, SRAF of only the anterior gastric side was performed, i.e. hemisection. The lesser curvature nerves were left intact, as was the pylorus. The rats were studied for 226 ± 5 days.

From the Centro de Investigaciones Pancreaticas (CIP), Buenos Aires, the Instituto de Investigaciones Gastroenterologia, Dr. Jorge Perez Companc, Buenos Aires, and the Pancreatic Research Laboratory, Mount Sinai School of Medicine (CUNY), New York.

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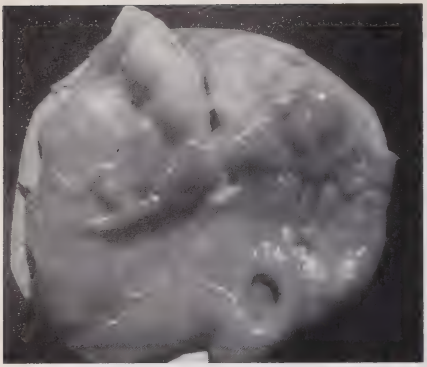


Fig. 1. Oval-shaped peptic ulcer in posterior wall of antrum with distinctive elevated borders and central fibrinous exudate.

Group 6. In 5 animals, body weight 477 ± 13 gm, seromuscular interrupted stitches with silk 6-0 were placed at the level of the antral-fundic junction in both the anterior and posterior gastric mucosa. Pyloroplasty was omitted. The animals were studied for 122 ± 1 days.

After operation, the rats were placed in individual cages and subjected to 12-h light/darkness intervals. They were all fed with standard Purina rat pellets. Following an observation period ranging from 122 to 225 days, rats were sacrificed under ether anesthesia. During autopsy, the wet weight of all abdominal organs was measured. The ratio of the wet gastric weight (gm) to body weight (kg) was considered the gastric index. A strip of the whole stomach wall comprising longitudinally the rumen, fundus, and antrum was fixed in formaldehyde and treated with hematoxylin-eosin and Mowry Grimelius stains. Immunohistochemical analysis of the G cells was performed with the PAP technique.

Preliminary morphometric determinations of the width of the gastric mucosa were made for the control subjects and the experimental animals.

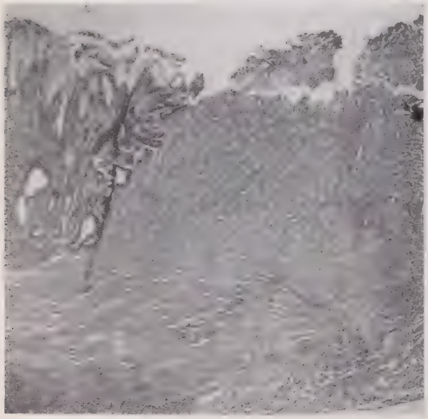
Statistical analysis was by Student t-test for nonpaired samples (2). A value of $p < 0.01$ was considered significant.

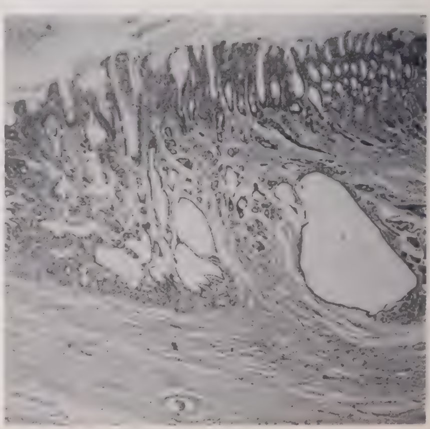
Results

Group 1. SRAF of both the anterior and the posterior gastric walls, with antral denervation and without pyloroplasty, induced chronic antral peptic ulcers in 56% of the cases (Fig. 1) after 139 ± 11 days.

The gastric index rose 53.5% with respect to the control group, i.e. control, 4.33 ± 0.11 gm/kg, SRAF, 5.55 ± 0.49 gm/kg. This increase was highly significant ($t = 6.32$, $p < 0.001$).

Group 2. A similar experimental protocol as the foregoing but with concurrent pyloroplasty triggered, within an interval of 183 ± 3.1 days, an antral peptic ulcer incidence of 25%. This percentage does not differ significantly from the previous one. Adding a pyloroplasty to the SRAF, however, prevented the marked increase of the wet weight of the stomach observed in series 1. The gastric index, 4.22 ± 0.29 gm/kg, was not significantly different from controls.





Group 3. SRAF sparing innervation of the antrum, without pyloroplasty, did not prevent the induction of chronic antral peptic ulcers. The incidence, assessed at a period of 221 ± 1.3 days, was 25%, not significantly different from series 1 and 2.

The gastric index, 5.55 ± 0.32 gm/kg, rose 28.2%, a significant increase ($p < .001$) in respect to controls, a result similar to that in group 2.

Group 4. Hemisection and reanastomosis of the posterior gastric wall, sparing the lesser curvature nerves and without pyloroplasty, in an evaluation carried out at an interval of 222 ± 2.01 days, induced an ulcer rate of 40% on the side subjected to SRAF. Moreover, it elicited 49.7% augmentation of the gastric index to 5.48 ± 0.40 gm/kg, which was significant ($p < 0.001$) with respect to controls.

Group 5. Hemisection and reanastomosis of the anterior gastric wall, preserving antral innervation and without pyloroplasty, evoked, after an interval of 226 ± 4.66 days, chronic antral peptic ulcers on the side subjected to SRAF in 25% of the cases, a rate not significantly different from rates in other groups. The gastric index, 5.15 ± 0.30 gm/kg, rose 47.03%, a significant increase ($p < 0.001$) in respect to controls.

Group 6. Placing a series of seromuscular interrupted stitches in both the anterior and posterior gastric mucosa at the level of the antral-fundic junction did not elicit antral peptic ulcers, at least within an interval of 122 ± 0.7 days. The gastric index was 5.88 ± 0.23 gm/kg, a 35.8% increase that was significant ($p < 0.001$) in respect to controls.

Discussion

It was surprising to find chronic peptic ulcers in either one or both aspects of the gastric antrum at the antral-fundic junction when this junction was severed (Figs. 1–9). The ulcers have all the histopathologic characteristics of human peptic ulcer, that is, loss of mucosal substance beyond the muscularis mucosae. Moreover, the study discloses that ulcer penetration becomes deeper as time passes. Usually, after a four-month period all antral layers are involved in the ulcer process. At autopsy, there is generally a marked inflammatory reaction with multiple adhesions between the gastric antrum and the neighboring organs—liver, pancreas, and spleen. Almost always, there is a marked inflammatory reaction in the regional lymph nodes. Observed from the luminal side (Fig. 1), the ulcers show distinct elevated margins. Ulcers are always found far from both the lesser and greater curvature and unrelated to the suture line. The size of the ulcers varies from 5 mm to 30 mm in diameter.

In contrast to the histopathologic characteristics of ulcers induced in this study are the superficial fundic ulcerations induced by various techniques attempting to mimic human peptic ulcer (3–5). The latter ulcerations have generally resulted from essentially three procedures: (a) through surgical interventions in the gastrointestinal tract; (b) by evoking alterations in the central nervous system; (c) by pharmacologic means (3–5). However, one experimental model, that of Alumets et al (5), somewhat resembles

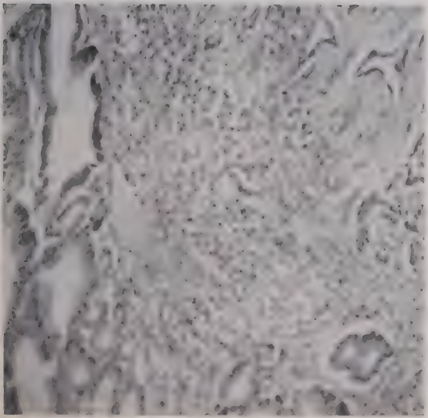
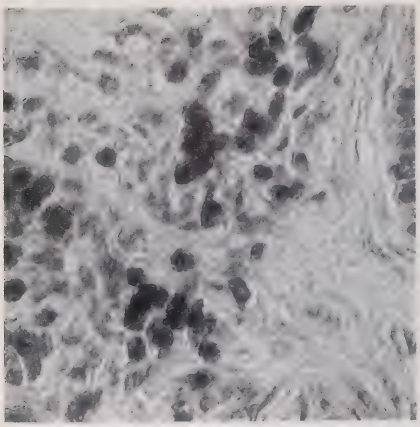
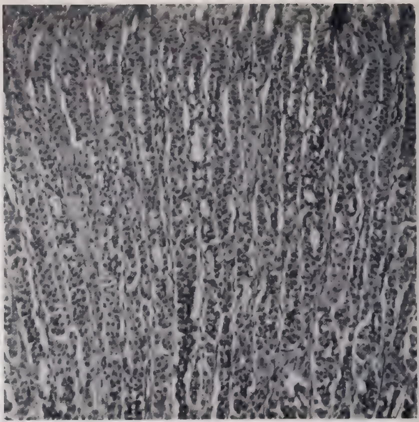
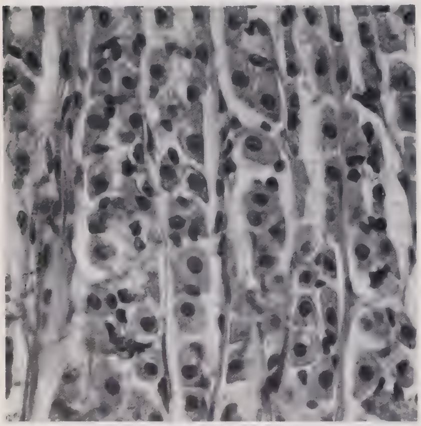


Fig. 2. Far left Ulcer margin and base showing transmural granulation tissue and necrotic debris on luminal side (original magnification 100 × HE). **Fig. 3. Middle left** Antral peptic ulcer margin showing submucosal glandular cyst formation and dysplastic changes (original magnification 100 × HE). **Fig. 4. Near left** High-power close-up: Submucosal glandular cyst formation revealing dysplasia and surrounding inflammatory infiltration (original magnification 100 × HE).







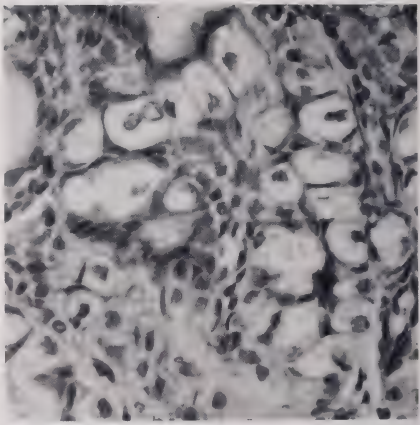


Fig. 5. Upper left Antral mucosa revealing focal hyperplasia of gastrin immunoreactive cells (original magnification 400 × PAP). **Fig. 6. Upper right** Fundic mucosa showing diffuse hyperplasia mainly of deep and medium (oxyntic cells) glands (original magnification 100 × HE). **Fig. 7. Lower left** Fundic tubular glands at its medium 1/3 showing parietal cell hyperplasia and cytoplasmic vacuolization (original magnification 400 × HE). **Fig. 8. Lower right** Parietal cells with marked cytoplasmic vacuolization through rupture of the cell membranes. The vacuoles lead to cyst formation (original magnification 400 × HE).

the present technique. These investigators reported a 10% incidence of superficial fundic erosions in rats subjected to antral-fundus disconnection and exclusion. They also reported a high (50%) mortality rate, whereas our SRAF rats had no mortality. Moreover, they did not observe any alterations in the gastric indices.

The gastric histopathologic alterations induced by SRA can be summarized as follows:

1. The antral ulcers have all the characteristics of nonexperimental human peptic lesions, inflammatory beyond the muscularis mucosa.
2. Development of the antral peptic ulcer seems to be unrelated to the degree of change in the width of the fundic mucosa.
3. Induction of the antral ulcer requires transection of the antral-fundic junction through all its layers. Thus, in experimental group 6,

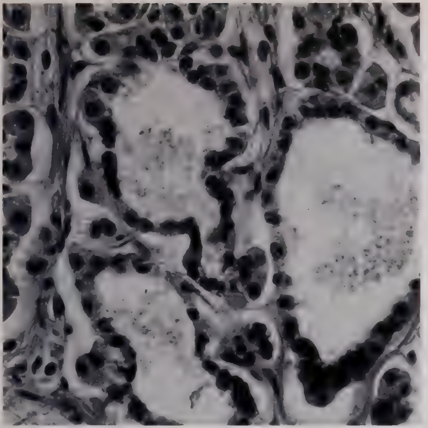


Fig. 9. Fundic glands showing dilated cysts lined by flattened parietal cells (original magnification 400 × HE).

placement of interrupted seromuscular stitches around the antral-fundic junction produced no antral ulcers despite elevation of the gastric index in respect to the controls.

4. After hemisection and reanastomosis of either the anterior or posterior antral-fundic junction (experimental groups 4 and 5), ulcers develop only on the gastric side subjected to SRAF. The opposite gastric wall shows no ulceration, despite increase in the width of the mucosa.
5. Although pyloroplasty associated with SRAF precludes an increase in gastric index, it does not prevent induction of antral peptic ulcers (groups 1 and 3).
6. The lesion is elicited whether the antral innervation is preserved or not (groups 1 and 3).
7. Maintenance of fundic-antral lumen continuity is essential to antral ulcer formation (5).

Summary

In adult male Wistar rats, section and reanastomosis at the antral-fundic junction (SRAF) in both gastric walls, cutting the lesser curvature nerves (antral denervation) and without pyloroplasty induces an incidence of chronic antral peptic ulcers of 56% in one or both stomach sides. The lesions penetrate the whole antral wall. The serosal inflammatory reaction usually involves the neighboring organs (liver, spleen, and pancreas) and the regional lymphatic chains. Periulcer dysplastic changes are observed. A significant increase (54%) of gastric wet weight develops. Histologic analysis discloses marked hyperplasia of the fundic mucosa, especially of the median and deep segments of the glandular tubules. The oxyntic cells are both hypertrophic and hyperplastic, with signs of hyperfunction. Neither preserving antral innervation nor concurrent pyloroplasty prevents ulcer formation. SRAF of just one gastric wall (hemisection) elicits an ulcer on the same side.

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Effects of Enteral Nutrition on Exocrine Pancreatic Secretion in Dogs

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Abstract

Nutritional assistance is advocated as part of the management in various pancreatic pathological states. Enteral nutrition is recommended in some of these cases in order to avoid some of the complications of parenteral nutrition. The effect of intraintestinal nutrition on exocrine pancreatic secretion was studied in a group of dogs. The dogs were surgically prepared with an isolated double-barreled jejunal segment and a Thomas cannula inserted in the duodenum opposite the main pancreatic papilla. The exocrine pancreatic secretion was collected through direct cannulation of the main papilla and analyzed for volume output and bicarbonate and amylase concentrations. Separate nutritional components (glucose 25%, intralipid and amino-acid solution) were administered by continuous drip into the isolated jejunal segment and their effect upon the exocrine pancreatic secretion was observed.

Hypertonic glucose significantly reduced pancreatic volume output, whereas fat caused an increase. Amino acids did not affect volume output. Fat caused an increase in bicarbonate as well as amylase concentration. Glucose decreased amylase concentration without affecting bicarbonate concentration. Amino acids had no effect on bicarbonate and amylase concentrations. These observations suggest that enteral hypertonic glucose has a depressing effect and fat has a stimulatory effect on exocrine pancreatic secretion.

Nutritional compromise occurs in various pancreatic pathological states, including pancreatitis, pancreatic fistula, and cancer of the pancreas. Nutritional assistance has been advocated for the management of these complications (1–3). Total parenteral nutrition (TPN), despite its tremendous advantages, may cause significant mechanical, septic, and metabolic complications (4). Therefore, in recent years interest has been renewed and experience amplified in using the gastrointestinal tract to provide nutrition in various surgical conditions. It has been shown that enteral feeding may in fact be as effective as parenteral feeding. It has also been observed that in patients with pancreatitis and pancreatic fistula, where exocrine pancreatic output depression is desired, TPN may play an additional therapeutic role (5–7). Despite numerous clinical reports attesting to the value of TPN, information on the mechanism of its action is scanty and controversial (5, 8).

We studied the effects of intraintestinal nutrition, using separate nutritional components, on the exocrine pancreatic secretion in dogs.

Materials and Methods

The study was performed on a group of 8 mongrel dogs. The dogs were operated on under general anesthesia and laparotomy was performed. A 40-cm segment of proximal jejunum was isolated and its proximal and distal ends brought out through the anterior abdominal wall as a double-barreled mucosal fistula. The conti-

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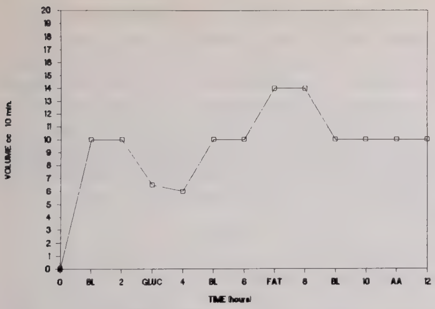

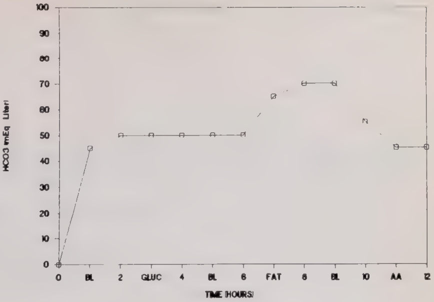

Fig. 1. Left Effects of nutritional components on pancreatic volume secretions. Each open square represents the mean of 16 animal observations (for statistical significance, see text). **Fig. 2. Right** Effects of nutritional components on bicarbonate concentration. See legend for Fig. 1.

nuity of the intact jejunum was reestablished by an end-to-end anastomosis. The duodenum was then mobilized, the accessory pancreatic duct isolated and ligated, and a Thomas cannula introduced into the duodenum (through a duodenotomy) opposite the main pancreatic papilla. After 14 days of recovery (during which the animals were fed on standard Chow), the series of observations began. Prior to each observation the animals were deprived of food, but not water, for 24 hr.

During observations the animals were put in a special stand which enabled proper handling and instrumentation of the jejunal fistula and Thomas cannula. Pancreatic juice was collected by means of a glass cannula introduced directly into the main pancreatic papilla (via the Thomas cannula) and analyzed for volume output and bicarbonate and amylase concentrations.

The secretory studies were performed under shedding of continuous intravenous secretion (Boots) (0.03 μ/kg per min), in order to have measurable amounts of pancreatic volume secretion. Thus, separate 10-min samples of pancreatic juice were collected until a plateau was reached in the rate of excretion. Following that, nutritional components were delivered by continuous drip using a catheter installed in the proximal mucosa fistula. The nutritional components, amino acid solution (Vamin, Vitreum, Sweden), glucose 25%, and fat (Intralipid, Vitreum, Sweden) in 200-ml volume, each dripped into the bowel during a period of 60 minutes. Following the infusion of each component, 200 ml of saline was dripped through the fistula.

Secretory studies were performed prior to, during, and after the various components dripped through the jejunal mucosal fistula.

Each animal served as its own control.

Results

Most of the solutions dripped into the isolated jejunal loop were retained (and probably absorbed) and the amount spilled out through the distal end was negligible. Statistical significance of results was assessed by the Mann-Whitney nonparametric test and Wilcoxon matched-pairs signed ranks test.

Volume Studies. Hypertonic glucose caused a significant ($p < 0.006$) decrease of 40% in volume and intralipid caused significant ($p < 0.01$) increase of 35% in the volume secretion (Fig. 1). Amino acid drip had no effect upon volume secretion.

Bicarbonate Concentration. During fat emulsion drip, bicarbonate concentration increased by 40%; hypertonic glucose and amino acid solution did not affect bicarbonate concentration (Fig. 2).

Amylase Levels. Amylase levels were significantly increased by 25% during fat administration and decreased by 50% during glucose treatment ($p < 0.01$ in both cases). Amino acids again had no effect on amylase blood levels (Fig. 3).

Hypertonic glucose caused a decrease in the pancreatic activity while fat emulsion caused an increase; amino acid solution had no significant effect.

Discussion

Our data suggest that various nutritional components given by drip into an isolated jejunal segment, in dogs, may affect pancreatic secretion in various ways. Hypertonic glucose reduces pancreatic volume output and amylase concentration, with a smaller decrease in bicarbonate concentration. Fat solution was observed to increase

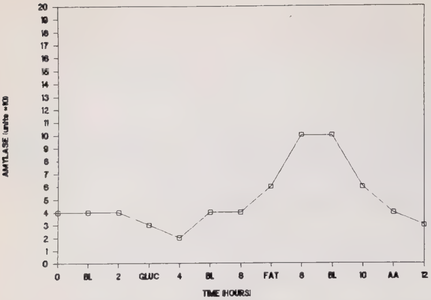

Fig. 3. Effects of nutritional components on amylase blood levels. See legend for Fig. 1.

volume output and contents, while amino acids had no effect upon pancreatic secretion.

Hypertonic glucose has been shown to suppress pancreatic secretion of volume and protein (9, 10) an action attributed to the increase in serum osmolality which probably inhibits secretion by solvent drag (11). It is most probable that the enterally administered glucose is absorbed into the circulation, thus causing the reported effects.

Information as to the effect of fat administration on pancreatic secretion is sparse and controversial. Konturek (12) observed an increase in pancreatic secretion in response to intraduodenal as well as intravenous fat. Meyer et al observed similar results with intraintestinal fat (13). It was also suggested by Henry et al (14) that fat has an indirect effect on secretin.

We have observed (15) that intravenous intralipid increases pancreatic excretory output, and our present observations are in accordance with the results of Konturek and Meyer on the effect of intraintestinal fat on pancreatic secretion.

These assumptions need further investigation.

Our results do not demonstrate any significant effect of amino acid solution on pancreatic secretion. The reports in the literature are controversial. Konturek (12) observed an increase in pancreatic protein secretion, whereras Johnson (6) reported the opposite.

Our study suggests that in the dog, enterally administered nutritional components and total parenteral nutrition affect pancreatic secretion in a similar way. Our observations further suggest that the recommended formula for treatment in various pathologic states in which pancreatic output depression is desired would be a high-glucose, high-protein combination, and that fat should be given in only minimal amounts that satisfy body needs for essential fatty acids.

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The Pancreas and Oxygen Consumption:

3. Do Steroids Improve Pancreatic O_2 Consumption Response To Hypovolemia?

Final Report

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Abstract

The data on pancreatic oxygen consumption (VO_2) of 4 female dogs (18–20.5 kg) subjected to hypovolemic shocks of 3-hr duration and receiving 35 mg/kg of methylprednisolone sodium succinate (MPSS) intravenously early in the course of bleeding were compared with data (previously published) on 11 canines who underwent the same operative protocol (controls, 4; hypovolemic shock alone, 4; MPSS alone, 3). Pancreatic VO_2 was obtained by multiplying regional blood flows ($\dot{Q}$), determined electromagnetically, times O_2 extraction provided by a Co-oximeter, and by adding up VO_2 for the head and tail of the pancreas.

Pancreatic VO_2 was significantly lower for the shock + MPSS group than for controls, except at the end of the second hour of hypovolemia. In conclusion, high-dose steroids do not improve pancreatic VO_2 during hypovolemic shock and appear of questionable benefit, at least on a metabolic basis, in the prevention and management of pancreatic damage induced by hypovolemia and/or low-flow states.

The purpose of this and the two preceeding reports (1, 2) is to assess possible pancreatic damage induced by hypovolemic shock in terms of pancreatic metabolic changes expressed as O_2 consumption (VO_2), and to study the effects of steroids thereupon. Two previous investigations in the laboratory came to the following conclusions: (a) pancreatic VO_2 significantly increased in the control group over a 3-hr period, but remained unaltered throughout hypovolemic shock of the same duration; (b) the administration of methylprednisolone sodium succinate (MPSS) to controls did not modify pancreatic VO_2, which continued to show a significantly increasing trend.

The purpose of the present investigation is to determine whether MPSS, given at a high dose early in the course of hypovolemic shock, modifies pancreatic VO_2 and could therefore warrant the use of steroids in the treatment or management of pancreatic damage observed during hypovolemia or low-flow states.

Materials and Methods

Four female dogs weighing between 18 kg and 20.5 kg (mean 18.6 kg) were the experimental subjects. The protocol was as follows: After a one-hour observation period to record parameters (cardiac output, regional blood flows, and oxygen extraction) to serve as reference

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TABLE

Cardiac Output, Regional Blood Flows, $(a\text{-}v)O_2$ Differences, and Oxygen Consumption in Shock + MPSS Group (Mean ± SE)

		Head of pancreas			Tail of pancreas			Pancreas (head + tail)	Hind limb		
	CO (L/min)	Q GDA (cc/min)	$(a\text{-}v)O_2$ (ml%)	VO_2 (ml/min)	Q SA (cc/min)	$(a\text{-}v)O_2$ (ml%)	VO_2 (ml/min)	VO_2 (ml/min)	Q FA (cc/min)	$(a\text{-}v)O_2$ (ml%)	VO_2 (ml/min)
Control (H_0)	3.54 ± 0.41	303 ± 61	3.5 ± 1.3	10.7 ± 1.9	246 ± 69	2.1 ± 0.9	5.2 ± 4.1	15.9 ± 3.8	360 ± 138	2.5 ± 0.9	22.9 ± 11.2
First hour (H_1)	1.18 ± 0.23	88 ± 38	8.6 ± 3.0	7.6 ± 3.6	125 ± 52	7.8 ± 2.9	9.7 ± 4.9	17.3 ± 2.3	78 ± 22	8.5 ± 2.9	6.6 ± 1.1
Second hour (H_2)	0.98 ± 0.15	107 ± 22	8.3 ± 3.1	8.9 ± 1.8	183 ± 102	7.0 ± 3.2	12.8 ± 6.6	21.7 ± 7.2	75 ± 18	8.0 ± 2.8	6.0 ± 1.2
Third hour (H_3)	0.89 ± 0.12	92 ± 16	8.8 ± 3.2	8.1 ± 2.7	140 ± 49	7.1 ± 3.2	9.9 ± 4.0	18.0 ± 4.5	68 ± 16	9.4 ± 3.2	6.4 ± 1.4

CO, cardiac output; Q, regional blood flows; GDA, gastroduodenal artery; SA, splenic artery; FA, femoral artery; $(a\text{-}v)O_2$, arterio-venous oxygen difference; VO_2, oxygen consumption.

values (control values, Ho, in Table), anesthetized animals were bled through the left common femoral artery (Fig. 1) into a heparinized bag until their mean arterial blood pressure (MABP) dropped to a value of 50 mm Hg, which took approximately 15 minutes. Once MABP had reached 80 mm Hg in the course of bleeding, MPSS was injected into a peripheral vein, using an infusion pump, over a period of 20 min. The injected dose amounted to 35 mg/kg. Three hours after the end of bleeding, shed blood was reinfused and accurately measured at this time.

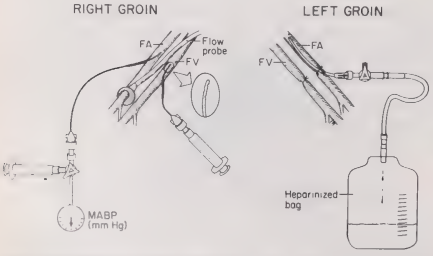
The operative protocol itself, which took approximately 90 min and was performed prior to the reading of any parameter, was in all points similar to the one used in our two previous investigations (1, 2). Briefly, pancreatic and hind limb VO_2 were calculated by multiplying regional blood flows ($\dot{Q}$) times the difference in arteriovenous O_2 content, or O_2 extraction, $(a\text{-}v)O_2$. Blood flows were determined electromagnetically by means of probes (Medical Electronics Inc, King NC) placed on the gastroduodenal (GDA), the splenic (SA), and the right common femoral (RFA) arteries; O_2 content was provided by a Co-oximeter (Model 282, Instrumentation Laboratory, Lexington MA) using blood samples originating from both right common femoral vessels (RFA + RFV), splenic (SV), and the superior pancreaticoduodenal (SPDV) veins (Figs 1, 2).

The data on the 4 dogs subjected to hypovolemia + MPSS were then compared with data on the control (n = 4) and hypovolemic (n = 4) groups (1), and on the MPSS-treated animals (n = 3) (2).

Statistical results (standard deviations and errors, *t* tests, and family regressions) were provided by a Hewlett-Packard 9815A calculator.

Results

Cardiac output (CO), regional blood flows in the GDA, SA, and RFA, O_2 extraction and O_2 consumption for head and tail of the pancreas, and hind limb, respectively $(a\text{-}v)O_2$ and VO_2, were measured in the 4 canines subjected to hypovolemic shock and MPSS (Table). Control values (Ho in Table) refer to the 5 determinations



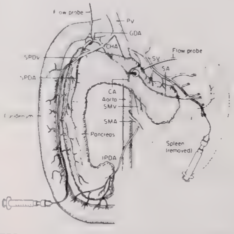
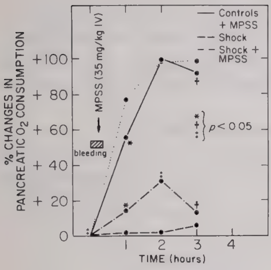


Fig. 1. **Left** Diagrammatic illustration of both groins: the right served for recordings (blood flow and samples), the left for bleeding and reinfusion. FA, common femoral artery; FV, common femoral vein; MABP, mean arterial blood pressure.

Fig. 2. Right Schematic operative protocol, canine pancreas, showing location of both electromagnetic flowprobes and epidural catheters. CA, celiac axis; CHA, common hepatic artery; SA, splenic artery; SMA, superior mesenteric artery; GDA, gastroduodenal artery; SPDA, superior pancreaticoduodenal artery; IPDA, inferior pancreaticoduodenal artery; PV, portal vein; SV, splenic vein; SMV, superior mesenteric vein; SPDV, superior pancreaticoduodenal vein.



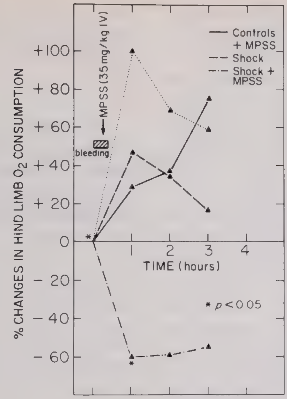


Fig. 3. Left Changes in pancreatic O_2 consumption, expressed as percentage change from initial value. Data are for 15 animals, 4 in this report and 11 in two prior reports (1, 2). Controls, 4; hypovolemic shock, 4; MPSS alone, 3; MPSS + shock, 4. **Fig. 4. Right** Changes in hind limb O_2 consumption, expressed as percentage change from initial value. Data as described for Fig. 3.

of all parameters taken prior to bleeding and MPSS. Within the shock + MPSS group, at the end of 3 hr of shock, just prior to reinfusion, CO fell to 75% of its initial value, $\dot{Q}$ GDA to 70%, $\dot{Q}$ SA to 43%, and $\dot{Q}$ RFA to 81%. The amount of blood withdrawn during the experiment averaged 519 ± 133 cc for the 4 animals.

Increases in pancreatic VO_2 were moderate over the 3-hr period and significant at the end of the second hour only (+31%) (Fig. 3). VO_2 for the head of the pancreas decreased throughout shock (−33% at H1, −26% at H2, and −35% at H3), whereas VO_2 by the pancreatic tail increased (+42% at H1, +100 at H2, and +78% at H3); pancreatic head and tail differed significantly from H2 on ($p < 0.001$).

O_2 consumption by the hind limb (Fig. 4) showed a decreasing trend during shock, significant at the completion of the first hour only (−60%, $p < 0.05$). Finally, within this shock + MPSS subgroup, pancreatic and hind limb VO_2 changes differed significantly throughout the experiment ($p < 0.01$ at H1 and H2, $p < 0.005$ at H3).

When considering similar time intervals for the four groups (controls, shock alone, MPSS alone, and MPSS + shock) the following observations can be made (Figs 3, 4):

1. Pancreatic VO_2 was significantly lower for the shock + MPSS group than for controls, except at the end of the second hour.
2. Pancreatic VO_2 did not differ significantly between animals subjected to steroids and shock and those receiving steroids alone; nor did it

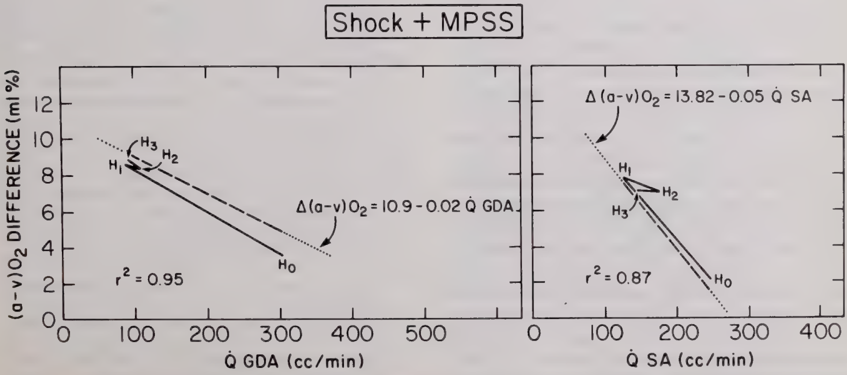


Fig. 5. Linear relationships between regional blood flow ($\dot{Q}$ GDA and $\dot{Q}$ SA) and O_2 extraction, (a-v)O_2, for head and tail of pancreas, in shock + MPSS group.

differ between canines subjected to shock and steroids and those undergoing shock alone.

3. Hind limb VO_2 was significantly lower in the shock + MPSS group than in any other; the only nonsignificant difference was at H3 between the steroid and shock + steroid group (+59% and −54% respectively; $p = 0.058$).

Discussion

Experimental studies investigating the use of steroids in hypovolemic shock emphasize the cardiovascular repercussion of these drugs, mainly changes in cardiac output or blood pressure, which appear to vary greatly according to the time and dose at which steroids are given in the course of shock (3–11). On the other hand, reports dealing with the effect of steroids on experimentally induced pancreatitis similarly diverge: whereas Kimura et al (12) found MPSS an aggravating factor in pancreatitis induced by an intraarterial injection of oleic acid in an isolated ex vivo perfused organ, Ferguson et al (8) showed pancreatic blood supply to be significantly improved when dexamethasone was given continuously throughout shock. Our findings probably fit somewhere in between these opposite conclusions.

The literature on pancreatic oxygen consumption was reviewed in the first of these 3 reports (1). In this overall series of 15 animals, resting pancreatic VO_2, that is, the mean of 5 values determined in each dog during one hour prior to bleeding, MPSS and/or simple observation (Ho in Table), averaged 10.9 ± 2.5 ml/min. Pancreatic VO_2 was obtained by adding up VO_2 for the head and tail of the pancreas and therefore did not include the uncinate process supplied by the inferior pancreaticoduodenal artery (IPDA, Fig. 2).

Were any changes brought about in pancreatic VO_2 when MPSS was added at the onset of hypovolemic shock? Little, if any. With the exception of a significant difference at the completion of the second hour of shock (+31% in the MPSS + shock group, vs + 4% in the shock group, $p < 0.05$), pancreatic VO_2 remained basically unaltered throughout shock, whether MPSS was added or not, and stayed significantly lower than control VO_2. A similar observation was noted when considering the effect of MPSS on GDA flow in shock (15). As within the shock group, increases in O_2 extraction were insufficient to maintain the higher levels reached by control pancreases (Fig. 5). In other words, MPSS does not appear to improve O_2 uptake by the pancreas, even when administered early and at high dosage in the course of bleeding. Pancreatic VO_2 did not differ either within both MPSS-treated groups, that is, whether animals were subjected to shock or not.

Conclusions

High-dose MPSS does not improve pancreatic VO_2 during hypovolemic shock and thus appears of questionable benefit, on a metabolic level, in the prevention and management of pancreatic damage induced by hypovolemia or low-flow states.

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The Role of the Pancreatic Enzymes in The Pathogenesis of Cholelithiasis

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Abstract

In 220 patients operated on for cholelithiasis, serum and gallbladder bile amylase levels were determined. An additional 20 patients who were operated on for other diseases constituted the control group.

In 139 patients (63.2%) out of 220, the bile amylase levels were elevated. Furthermore the elevated levels of the isoenzyme α1-amylase in bile samples obtained (a) from the gallbladder of 35 patients randomly chosen from this group of 139 and (b) from the common bile duct of 34 patients with T-tubes suggest that amylase originates exclusively from the pancreas and not from any extrapancreatic source.

It is possible that biliary reflux of pancreatic enzymes may initiate inflammation on the mucosa of the gallbladder and could play a role in the pathogenesis of cholelithiasis.

The high incidence of cholelithiasis and its serious complications constitutes a continuous problem for both patients and doctors. In the past, substantial progress has been made in the identification of factors which contribute to gallstone formation. Mechanisms such as increased cholesterol secretion by the liver, reduction of the bile salt pool through excessive loss secondary to inadequate intestinal absorption, abnormal absorption of bile salts by the inflamed gallbladder, the use of drugs (estrogen, etc.) which affect bile secretion and saturation, and increased bile pigment production associated with hemolytic disease have been proved to be the main factors that cause the production of supersaturated bile and therefore gallstones (1, 2). Pressure in the pancreatic duct is known to be greater than that found in the bile duct (3–5). Some authors have stated that inflammation of the gallbladder wall is initiated by the action of pancreatic enzymes which may reflux into the biliary tract because of this pressure difference (6).

The present study was undertaken to determine the role of pancreatic enzymes in the pathogenesis of gallstone disease.

Material and Methods

A total of 220 patients who underwent cholecystectomy in the First Propaedeutic Surgical Clinic of Athens University Medical School during the period October 1983–December 1985 were included in this study. The control group consisted of 20 additional patients who were operated on for diseases other than cholelithiasis (peptic ulcer, colorectal cancer, gastric cancer). The following groups of patients were excluded: (a) Patients who underwent cholecystectomy but in whom a sample of gallbladder bile could not be taken due to technical difficulties. (b) Patients with obstruction of the cystic duct (empyema or gallbladder containing mucoid material), because in these patients entry of the regurgitated pancreatic enzymes into the gallbladder is impossible. As a matter of fact, no amylase was found. (c) Patients with diagnosed liver diseases, liver neoplasms, hydatid cyst disease, and reoperations in the biliary tract, to exclude any possibility of pancreatic enzymes entering the biliary tract from any source other than the pancreas.

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TABLE 1

Perioperative Complications in 220 Patients with Gallbladder Stones

Complication	Number of patients
Obstruction of the biliary tract	51
acute cholecystitis obstruction of the cystic duct	18
Choledocholithiasis	33
History of acute pancreatitis	17
Chronic cholecystitis	152
Total	220

TABLE 2

Amylase Activity in Gallbladder Bile and Serum in 220 Patients Operated on for Cholelithiasis

	Elevated amylase	Normal amylase	Total
Men	37 (55.2%)	30 (44.8%)	67 (30.45%)
Women	102 (63.2%)	51 (33.3%)	153 (69.55%)
Total	139 (63.2%)	81 (36.8%)	220 (100%)

Serum amylase activity ≦8 units Wohlgemuth.

TABLE 3

Gallbladder Bile Amylase Activity in 51 Patients with Some Degree of Biliary Tract Obstruction and in 152 Patients without Obstruction

	Elevated amylase	Normal amylase	Total
Cholelithiasis with obstruction of biliary tract	17 (33.3%)	34 (66.7%)	51
Chronic cholelithiasis	107 (70.4%)	45 (29.6%)	152

$P < 0.001$.
Serum amylase activity ≦8 units Wohlgemuth.

(d) Patients with chronic hemolytic disease, in whom presence or absence of increased amylase activity in the gallbladder bile is unlikely to be the main contributing factor in gallstone formation. (e) Patients with preoperative serum amylase activity higher than 8 units Wohlgemuth.

Of the total, 67 patients were men (mean age 58.8 years, SD 7.2 years) and 153 women (mean age 55.1 years, SD 8.7 years). One hundred seventy-eight patients underwent cholecystectomy to correct acute or chronic cholecystitis, with cholelithiasis. In 42 (19%) patients, both cholecystectomy and common bile duct exploration were performed. In 51 of 220 patients, cholelithiasis had caused some degree of obstruction of the cystic duct without empyema (18 cases) or choledocholithiasis with or without obstructive jaundice (33 cases). Seventeen patients had a history of one or more episodes of pancreatitis in the recent past which was verified during the operation (Table 1).

Measurements. In all patients both preoperative serum and perioperative gallbladder bile levels of amylase were measured. Serum amylase activity was considered to be normal if it was under 8 units Wohlgemuth; gallbladder bile amylase activity was considered elevated if it was over 20 units Wohlgemuth. Gallbladder bile was obtained during operation by insertion of a large-bore needle into the lumen and aspiration of the contents, prior to any manipulation of the organ.

In 42 patients with T-tubes following exploration of the common bile duct, multiple samples of bile were obtained and the value of amylase activity was calculated. In 34 of 42 patients (80.9%) with increased amylase activity, the isoenzyme α-1-amylase was determined by the use of Monotest α-1-amylase PNP.

In 35 patients chosen at random from the 139 with elevated gallbladder amylase activity, the isoenzyme α-1-amylase (produced exclusively by the pancreas) was determined.

In the control group, both serum and gallbladder bile amylase were measured by the Wohlgemuth method perioperatively.

Results

In 139 patients of 220 (63.2%), gallbladder amylase activity was elevated (amylase >20 units Wohlgemuth). In these patients the serum amylase activity was less than 8 units Wohlgemuth. Thus the level of gallbladder amylase in 139 patients was 2 to 250 times greater than the level of serum amylase (Table 2). It is obvious that in the majority of the patients suffering from cholelithiasis, amylase and therefore the rest of the pancreatic enzymes are increased in the gallbladder bile.

Comparison of the level of gallbladder bile amylase in the group of 51 patients with some degree of obstruction of the biliary tract and the group of 152 without obstruction (Table 3) showed significant statistical difference ($P < 0.001$) in that the level of amylase is increased in 66.7% of the patients of the first group compared to 29.6% of the patients of the second group.

In the majority of patients with a history of acute pancreatitis due to cholelithiasis (88.2%), the level of bile amylase was higher than in the group of 152 patients without any complications (Table 4) and higher than in the group of 51 patients with obstruction of the biliary tract (Table 5). There was a significant statistical difference ($P < 0.001$) between the group of 15 patients with histories of pancreatitis and the group with obstruction of the biliary tract (Table 5).

The determination of amylase concentration in bile as taken from the T-tube in 42 patients indicated that in this group, the percentage of patients with increased values of amylase was greater than in the remaining 152 patients with single cholelithiasis (Table 6). These findings are consistent with the observation that the pressure difference between the pancreatic duct and biliary tract is further increased by the insertion of a T-tube after choledochotomy. This permits freer reflux of pancreatic juice into the common bile duct than under normal conditions. Furthermore, the determination of the isoenzyme α-1-amylase proves that the source of amylase was the pancreas (Table 6).

In 35 randomly chosen patients with bile amylase levels elevated as measured by the Wohlgemuth method, the increased levels of α-1-amylase determined by the use of Monotest α-1-amylase PNP indicate that amylase originates exclusively in the pancreas and not from any extrapancreatic sources (Table 7).

The concentration of amylase in the gallbladder bile of the control group patients was under 2 units Wohlgemuth, suggesting that in patients without cholelithiasis, amylase activity in the gallbladder bile is absent.

TABLE 4

Gallbladder Bile Amylase Level in 17 Patients with History of Acute Pancreatitis and in 152 Patients with Simple Cholelithiasis

	Elevated amylase	Normal amylase	Total
History of pancreatitis	15 (88.2%)	2 (11.8%)	17
Simple cholelithiasis	107 (70.4%)	45 (22.6%)	152

$P > 1$

Serum amylase ≦8 units Wohlgemuth.

TABLE 5

Gallbladder Bile Amylase Level in Patients with Obstruction of Biliary Tract and those with a History of Acute Pancreatitis

	Elevated amylase	Normal amylase	Total
History of pancreatitis	15 (88.2%)	2 (11.8%)	17
Obstruction of biliary tract	17 (33.3%)	34 (66.7%)	51

$P < 0.001$

Serum amylase ≦8 units Wohlgemuth.

TABLE 6

Amylase Levels in Bile Obtained from T-Tube following Common Bile Duct Exploration

Amylase level	No. of patients	Wohlgemuth units	Monotest α-1-amylase PNP
Elevated	34 (80.9%)	256–2048	980–6600
Normal	8 (19.1%)	0–2	

Serum amylase ≦8 units Wohlgemuth.

Discussion

The close anatomic and functional relationship between the biliary tract and the pancreas suggests that the presence of pancreatic enzymes in the gallbladder bile may play an important role in the pathogenesis of cholelithiasis (2).

In 220 patients who underwent an operation for cholelithiasis, serum and gallbladder bile amylase levels were determined. In 139 patients (63.2%), bile amylase level was elevated (over 20 units Wohlgemuth) and serum amylase level was less than 8 units Wohlgemuth. The same findings were reported in 1979 by Anderson et al, who in 93 patients found 67% elevated amylase level in gallbladder bile in cases of cholelithiasis (6). It would not be surprising to find that other pancreatic enzymes would be elevated in the gallbladder bile. Indeed, Paris et al (12) and Anderson et al (6) found elevated level of lipase in the gallbladder bile in 87.5% and 66% of their series.

Experimental studies have indicated that pancreatic enzymes refluxing into the biliary system produce severe inflammatory changes (7, 8). In patients with acute pancreatitis, the diffusion of trypsin into the pancreatic parenchyma is known to induce severe alterations of the microcirculation and increase capillary permeability. A similar action occurs in the mucosa of the gallbladder when trypsin regurgitates into the biliary tree (9). The diffusion of lipase into the intercellular space shatters the lipid components of membranes and disrupts cellular integrity (6). Phospholipase A, a major constituent of refluxing pancreatic juice, disrupts the cellular structure similarly to lipase and in addition converts lecithin to lysolecithin. Both phospholipase A and lysolecithin are known to exert potent lytic effects on the gallbladder mucosa (7, 8). On the other hand, the presence of amylase in the gallbladder bile by diffusion through the liver capillaries can be excluded by the works of Korotko et al (10) and Levitt DM et al (11), even though Paris et al

TABLE 7
Gallbladder Bile Levels of Amylase: Wohlgemuth Method and Monotest α-1-amylase PNP

No. of Patients	Amylase level	
	Wohlgemuth	Monotest α-1-amylase PNP
5	20–100	112–1276
8	100–200	928–1636
14	200–500	945–4200
8	500	3842–6600

$P < 0.001$
Serum amylase ≦8 units Wohlgemuth.

(12) and Kurzanov (13) came to an opposite conclusion.

The evidence supporting pancreatic juice refluxing into the biliary tract is strong and includes:

- According to Opie's studies, there is a common terminal ampulla of pancreatic and biliary tract and free communication between the two systems in 60–90% of human beings. This anatomic relation explains the pathogenesis of acute pancreatitis which is caused by the impaction of a gallstone in the ampulla of Vater.
- The possibility of cannulation of the biliary and pancreatic duct by the use of a side-view endoscope enables the determination of pressures which exist in both ducts. It was found that the pressure inside the common bile duct is always less than the pressure inside the pancreatic duct. This pressure difference and the free communication of the two ducts permits the reflux of pancreatic juice into the common bile duct (5, 14).
- Finally, Levitt et al (11) and Rosenblum et al (15), using as experimental animals, rabbits in which there is no anatomic communication between the biliary and pancreatic ducts, found no radioactivity in the liver, the gallbladder, and the pancreas following IV radiolabled amylase and ribonuclease as well as after injecting these enzymes into the duodenum. These observations deny the filtration of amylase and ribonuclease from the blood through the liver or pancreas as well as indicate the absence of enterohepatic or enteropancreatic circulation of the above enzymes. Therefore the amylase which is found in the gallbladder bile must originate exclusively from the pancreas by reflux into the common bile duct.

The above contentions are supported by our study. The comparison of the values of amylase levels between the group of 51 patients with obstruction and the group of 152 patients without obstruction (Table 3) proves that the percentage of patients with elevated amylase is minimal in the first group ($P < 0.001$) since reflux is not possible in the face of obstruction.

On the other hand, if the group of 17 patients with a history of acute pancreatitis is compared with the group of the 152 patients without any complication (Table 4), as well as with the group of 52 patients with obstruction of the biliary tract (Table 5), significant statistical difference ($P < 0.001$) occurs only in obstructed patients. The latter observation indicates that patients with a history of acute pancreatitis have a higher percentage communication between the bile and pancreatic duct than the other patients.

The most convincing evidence favoring pancreatic reflux into the biliary system is the determination of concentrations by the α-1-amylase method, since this isoenzyme is produced exclusively in the pancreas. The pathogenetic sequence would be as follows: activated pancreatic ferments, that is, trypsins, lipases, phospholipase A, and so on, would cause an inflammatory reaction in the gallbladder mucosa. Bile would under stasis, concentration, conversion of lecithin to lysolecithin, progressive instability of the supersaturated cholesterol solution which, combined with an alteration of mucosal mucins, would lead to precipital of cholesterol and, thus, gallstone formation.

Conclusion

Evidence has been presented indicating that reflux of pancreatic juice into the biliary tract is a pathogenetic mechanism for gallbladder disease and gallstone formation.

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Microbiologic Correlates Underscoring The Diagnosis of Opportunistic Infections In Patients with AIDS

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Abstract

Severe opportunistic infections characterize and complicate the course of individuals with the acquired immune deficiency syndrome (AIDS). The specific infectious agents encountered in the setting of AIDS, however, have been encountered in other immunocompromised patients. This review, based largely upon our experiences in the microbiologic diagnoses of opportunistic infections in patients with AIDS, focuses on those subtleties that distinguish the microbiologic presentation of the infectious agent or unusual clinical symptomatology attributable to an isolate in this setting.

During the past decade the specific etiologic agents of several infectious diseases have been identified. Paramount among these breakthroughs were the resolving of the microbiologic basis of Legionnaire's disease (*Legionella pneumophila*), antibiotic-associated enterocolitis (*Clostridium difficile*), toxic-shock syndrome (*Staphylococcus aureus*), Lyme disease (*Borrelia burgdorferi*), and most recently the acquired immune deficiency syndrome (AIDS) (human immunodeficiency virus (HIV)). The specific microbiologic cause for each of the preceding clinical entities is definitive and diagnosis may be achieved by demonstrating the infectious agent directly or by culture of involved tissues; by assay for toxin; or by demonstrating a specific antibody response to the microbial offender.

Interestingly, with AIDS, the recovery of HIV or the demonstration of an antibody response to its presence is not conclusive in diagnosing AIDS, because only a fraction of individuals exposed to this virus have so far developed symptoms of AIDS (1). Instead, the diagnosis of AIDS and AIDS related disorders is made through a constellation of opportunistic infections and malignancies. Thus, in this instance, while infection with the putative viral agent is suggestive, visualization or isolation of one or more of the opportunistic pathogens closely linked to this syndrome, for instance *Pneumocystis carinii,* is diagnostic in an appropriate clinical setting. Additionally, from the microbiologic viewpoint, the characteristic presentation of these agents is frequently unlike that observed in patients immunodeficient due to underlying disease or immunosuppressive therapy or both. In this review we strive to draw particular attention not only to the infectious agents accounting for the extreme morbidity and mortality in AIDS, but to subtleties in their presentation that are strikingly associated with AIDS. Additionally, we address the utility of serology as a diagnostic adjunct for infections caused by the numerous bacterial, fungal, parasitic, and viral agents in AIDS.

Materials and Methods

Specimens from AIDS patients submitted for microbiologic analysis were obtained either by fiberoptic bronchoscopy under local anesthesia or

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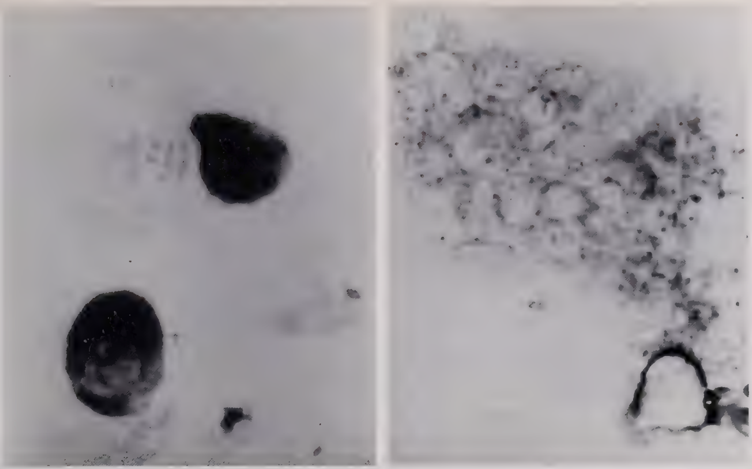


Fig. 1. Giemsa-stained smear of open lung biopsy specimen of renal transplant patient with interstitial pneumonia showing (**left**) single cyst of *Pneumocystis carinii* as contrasted (**right**) to densely packed cysts observed in bronchial brushings of a patient with AIDS.

by colonoscopy. Touch prints on glass slides were prepared at the time of the procedure. In the laboratory smears were individually stained by Gram, Giemsa, and Kinyoun methods, and evaluated microscopically. Other specimens submitted for the isolation of microbial pathogens were processed according to standard procedures.

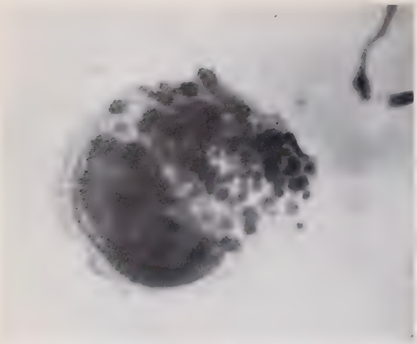
Results and Discussion

The specific opportunistic infections seen in AIDS patients have all been encountered in other immunocompromised patients. Heading the list as the premiere opportunistic offender is *Pneumocystis carinii,* a protozoan parasite. Microbiologically, in Giemsa-stained smears of bronchial brushings and biopsies, numerous dense clusters of *P. carinii* in every stage of its life cycle—from free crescent-shaped trophozoites, to viable cysts containing up to 8 sporozoites, to cysts undergoing degeneration—may be observed (Fig. 1).

Cytomegalovirus (CMV) infections are common in homosexual men and also in those with AIDS. CMV pulmonary infection may be diagnosed histologically, through culture, or by evaluation of Giemsa-stained smears of bronchial brushings or open lung biopsy specimens. In bronchial specimens, the presence of enlarged cells with intranuclear inclusion ("owl's eye") or cells with large, discrete, oval, dark blue intracytoplasmic inclusions 1.5–7.0 μm in diameter (2) (Fig. 2) is strongly suggestive of CMV infection. Confirmation of the morphologic finding can be achieved through tissue culture or by immunofluorescence.

Use of Giemsa-Stained Smears. The direct examination of Giemsa-stained smears of clinical material has also proven to be of extreme value in the diagnosis of toxoplasmosis, histoplasmosis, and cryptococcosis. In these instances, visualization of trophozoites, singly or in clusters, of *Toxoplasma* (Fig. 3), small oval yeast bodies of *Histoplasma* within histiocytes, or budding yeast cells encircled by a purplish halo characteristic of *Cryptococcus* have all proven diagnostic. The presence of multinucleated giant cells in Giemsa-stained smears of bronchial secretions or scrapings of vesicular lesions (Tzanck preparation, Fig. 4) is of high predictive value for *Herpes simplex* or Varicella zoster infection (3).

Although rarely reported prior to the onset of AIDS, infections of the human gastrointestinal tract with the sporozoan protozoan *Cryptosporidium* has emerged as a significant clinical entity complicating the course of patients with AIDS (4). Subsequent to its recognition as an agent of protracted diarrhea in immunodeficient individuals, *Cryptosporidium* was also shown to infect the upper respiratory tract as well (5). Because the diagnostic structure is the cryptosporidial oocyst containing up to four crescent sporozoites, when occurring in the upper respira-



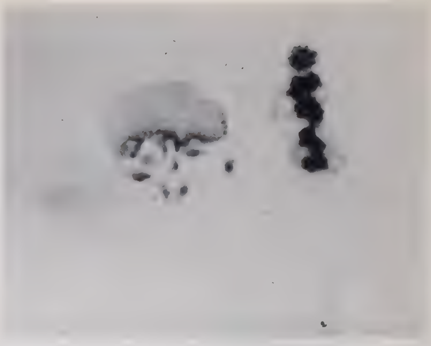


Fig. 2. Left Enlarged pulmonary cell showing numerous discrete oval cytoplasmic inclusions suggestive of cytomegalovirus. (Giemsa stain, original magnification 1000 ×). **Fig. 3. Right** Trophozoites of *Toxoplasma gondii* observed directly in imprint of brain biopsy specimen. (Giemas stain, original magnification 1000 × , *courtesy Dr. Joseph Masci*).

tory tract, this structure may easily be confused in Giemsa-stained smears with cysts of *P. carinii.* We have observed on two occasions cryptosporidial oocysts in Giemsa-stained smears of bronchial and gastrointestinal (Fig. 5) specimens from AIDS patients which bear a striking resemblance to the cysts of *P. carinii.* Subtle morphologic features raising an index of suspicion for *Cryptosporidium* include a distinct halo surrounding the oocysts and up to four red-staining sporozoites. If sporozoites are not clearly visible, the chromatin material within the oocyst stains red and is reminiscent of that observed with malarial parasites. Confirmation and differentiation from *Pneumocystis* may be achieved by demonstrating the acid-fast staining characteristic of the *Cryptosporidium* oocyst (6).

Mycobacterium avium-intracellulare has long been recognized as a nontuberculous mycobacterial species capable of causing primarily pulmonary and rarely disseminated infections in immunocompromised patients. In AIDS patients, however, this nontuberculous species has emerged as a scourge producing disseminated life-threatening infections (7). Histologically, in contrast to every other mycobacterial infection except leprosy, astounding numbers of *M. avium-intracellulare* may be observed in biopsy specimens in the absence of typical granuloma formation to highlight their presence (8). As a result of their unbridled multiplication, we have observed numerous highly refractile slightly curved bacilli in Giemsa-stained smears of bronchial brushings from an intravenous drug abuser who developed pulmonary *M. avium-intracellulare* infection. Subsequent Kinyoun stains (Fig. 6) of the same material revealed the acid-fast nature of the observed bacilli. The use of mycobacterial-specific nucleic acid probes has shown the majority of our isolates recovered from patients with AIDS to be *M. avium* (8a).

M. avium-intracellulare has also proven to be a significant gastrointestinal pathogen in patients with AIDS producing a diarrheal syndrome (9, 10). Kinyoun stain of colonic biopsy will reveal numerous acid-fast bacilli in densely packed bundles. In homosexual patients with AIDS, because the gastrointestinal tract may be involved early with *M. avium-intracellulare,* the anorectal area has been proposed as a potential portal of entry for this microbial species and venereal transmission as a mode of acquisition (10).

Unusual Prodromal Infections. Currently, the diagnosis of AIDS is based primarily upon the presentation of a severe opportunistic infection or an unusual malignancy, or both, in a previously healthy patient, without a known immunodeficiency. As stated earlier, no single laboratory test, including a positive assay for anti-HIV antibody, is pathognomonic for AIDS. However, many patients in the prodromal state of AIDS may present with unusual infections suggesting impairment in cell-mediated immunity. Among these are recurrent salmonella infections and oral candidiasis.

Salmonella infection, especially bacteremia, is an infrequent complication in drug addicts, in patients without AIDS who have a cellular immune dysfunction, and in male homosexuals, despite the latter's enhanced risk for the acquisition of other enteric pathogens such as *Shigella* or *Entamoeba histolytica.* In patients with AIDS, recurrent or protracted nontyphoidal *Salmonella* bacteremia may be one of the earliest manifesta-

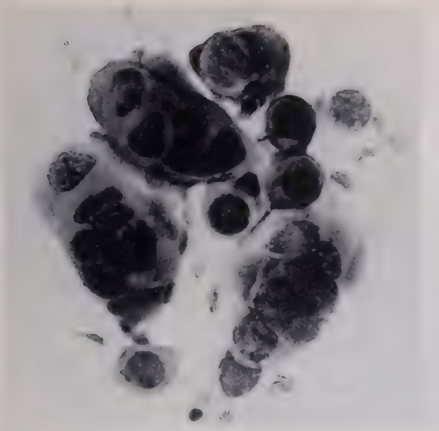


Fig. 4. Giemsa-stained smear (Tzanck preparation) of scraping of vesicular lesion showing multinucleated giant cells and intranuclear inclusions characteristic of herpesvirus infection (original magnification 1000 ×).

tions of the acquired immune deficiency syndrome. Bottone, Wormser, and Duncanson (11) documented four patients (two drug addicts, two homosexuals) who had repeated episodes of either *S. typhimurium* or *S. enteritidis* bacteremia and/or urinary tract infection prior to the development of other manifestations of the acquired immune deficiency syndrome such as Kaposi's sarcoma or multiple opportunistic infections. Since the publication of their report, several additional articles noting this association have appeared (12, 13, 14, 14a). Several features of salmonellosis in patients with AIDS include a high prevalence of infection in this patient population as contrasted to the general population, including homosexual men: the inordinate incidence of bacteremia, and the recurrent pattern of infection despite appropriate antibiotic therapy.

Although we have encountered several AIDS patients with dysentery caused by *S. flexneri*, none of our patients was bacteremic. However, Glaser and colleagues (15) described 5 patients with AIDS who in the course of *S. flexneri* gastroenteritis also developed *S. flexneri* bacteremia. In two patients, bacteremia occurred 3–7 months prior to the diagnosis of AIDS and developed concomitantly with Kaposi's sarcoma or opportunistic infections. Thus, as with non-typhoidal *Salmonella* bacteremia, shigellemia occurring in previously healthy individuals may signal an acquired immunodeficiency.

Oral candidiasis is seldom observed in healthy individuals. In a study conducted by Klein and associates (16) on unexplained oral candidiasis in patients at risk for AIDS, more than 50% of these patients went on to acquire a major opportunistic infection or Kaposi's sarcoma within 1 to 23 months after developing oral candidiasis. Microbiologic confirmation of intraoral lesions can be obtained by visualizing characteristic blastospores and pseudohyphal elements on direct examination of scrapings treated with potassium hydroxide, or by Gram or Giemsa stain. Thus, as with recurrent salmonellosis, oral candidiasis occurring in previously healthy individuals, especially those in a high risk group (e.g., IV drug abusers, homosexual men), may serve as an early manifestation of AIDS prior to the onset of more severe opportunistic infections or neoplasia. Indeed, such microbial harbingers of AIDS could well pave the way for early therapeutic intervention.

TABLE 1

Opportunistic Infections Documented in AIDS Patients

Agent	Major Site of Involvement
Protozoal	
Pneumocystis carinii	Pulmonary
Toxoplasma gondii	Brain, pulmonary
Cryptosporidium	Gastrointestinal, respiratory tract
Isospora belli	Gastrointestinal
Viral	
Cytomegalovirus	Pulmonary, disseminated
Herpes simplex	Perianal ulcerations, disseminated
Adenovirus	Urinary tract
Progressive multifocal leukoencephalopathy virus	Brain
HIV*	T-4 (helper) lymphocytes
Fungal	
Candida albicans	Mucocutaneous, esophagitis
Cryptococcus neoformans	Central nervous system, pulmonary, disseminated
Histoplasma capsulatum	Disseminated
Aspergillus	Pulmonary, disseminated?
Pityrosporum sp.	Seborrheic dermatitis
Mycobacterial	
M. tuberculosis	Disseminated
M. avium-intracellulare	Gastrointestinal, disseminated
M. xenopi	Pulmonary disseminated
Bacterial	
Listeria monocytogenes	Bacteremia
Nocardia asteroides	Pulmonary disseminated
Legionella pneumophila	Pulmonary, brain
Salmonella (nontyphoidal)	Bacteremia, gastrointestinal
Shigella flexneri	Gastrointestinal, bacteremia
Shigella sonnei	Gastrointestinal, bacteremia?

* Human immunodeficiency virus.

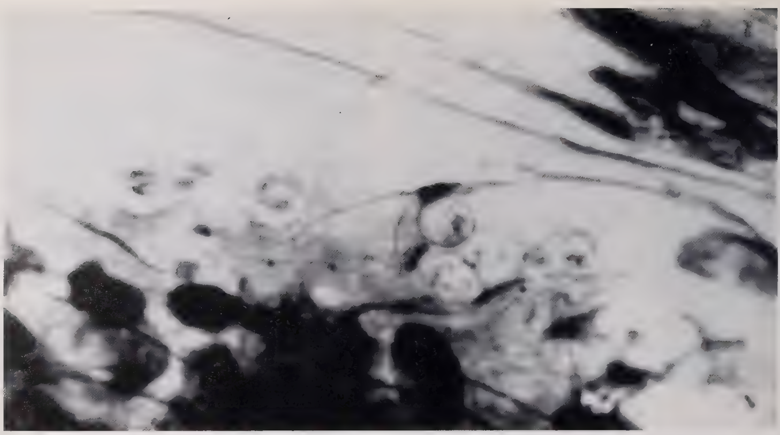


Fig. 5. Giemsa-stained smear of colonic biopsy of AIDS patient with protracted watery diarrhea showing numerous oocysts of *Cryptosporidium* surrounded by a halo. Note marked similarity to cysts of *P. carinii* (original magnification 1000 ×).

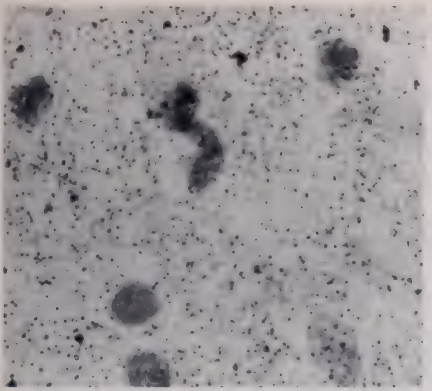
In patients with AIDS one may anticipate infections not only with many of the aforementioned microorganisms, but also with those not yet identified but whose removal from the human body is mediated through T-cell activity. In this regard reports of less frequently isolated agents may appear.

Listeria monocytogenes, a facultatively intracellular microorganism, is a frequent cause of bacteremia and meningitis in patients with defects in cell-mediated immunity. In patients with AIDS, *Listeria* appears just on the threshold of expression as an opportunistic pathogen and has recently been described as causing bacteremia in two of 226 AIDS patients seen at the Memorial Sloan-Kettering Cancer Center as of March 1984 (17). In our institution to date (December 1987), in well over 300 patients with AIDS, there has been only a single case of listeriosis. Nevertheless, infections with this microorganism, as well as *Strongyloides stercoralis* and *Legionella pneumophila,* are real threats in this patient population.

Correlative to the above, one of the intriguing aspects of the profound immunosuppression seen in AIDS victims is infection caused by less virulent microbes not commonly recovered from normal or other immunocompromised (non-AIDS) persons. These infectious agents have reduced virulence for the normal host but may cause serious infections in AIDS patients. Their virulence may be enhanced by their introduction through atypical routes of entry, for example rectally, or through blood. Of particular interest is the striking association of adenovirus serotype 34,35 (AD34, AD35) with urinary tract infections (18, 19), of infections with capsule-deficient cryptococci (20, 21), and of enteritis caused by unusual campylobacter-like organisms (22).

The urinary recovery of adenovirus serotype 34,35 appears to be significantly associated with AIDS patients. This virus can persist in their urine for periods exceeding 12 months. In most of these instances elevated antibody titers have not been detected (see below). In studies performed to date, this combined serotype has not been found in high frequency in normal populations and its seeming predilection for AIDS patients seems unique. Fifteen of 26 isolates (including 3 from Mount Sinai) from the urine of these patients expressed either or both of the AD 34 and AD 35 hemagglutinins on the cell surface (18, 19). Perhaps the numerous cellular alterations noted in patients with AIDS affect or expose urinary tract epithelial surfaces favoring colonization by these rarely encountered adenovirus serotypes. An interesting sidelight to this finding is that the isolation of AD 34,35 from severely immunocompromised (non-AIDS) individuals predated the discovery of the acquired immune deficiency syndrome by 4 to 5 years.

Bottone and colleagues (20, 21) have isolated a number of poorly encapsulated strains of *Cryptococcus neoformans* from the cerebrospinal fluid of patients with AIDS who had cryptococcal meningitis. These isolates, all recovered from pa-



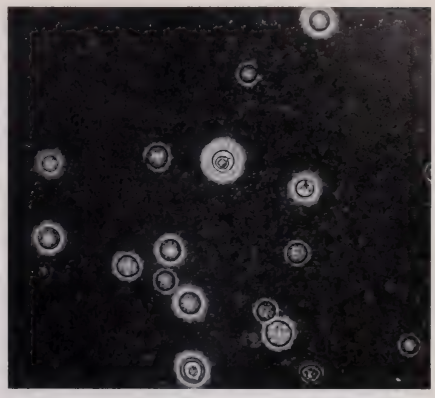


Fig. 6. Innumerable irregularly acid-fast staining, slightly curved, beaded bacilli of *Mycobacterium avium-intracellulare* observed in bronchial brushings of a patient with AIDS. **Fig. 7.** Direct India-ink preparation of cerebrospinal fluid of a patient with AIDS and meningitis showing poorly encapsulated *Cryptococcus neoformans*.

tients in the NYC area, have significantly smaller capsules (Fig. 7) than their counterparts recovered from the spinal fluid of non-AIDS individuals. This association may suggest preferential infection of patients with AIDS by a morphologically distinct *C. neoformans*. Similar findings have been reported by Gal et al (21a).

Pityrosporum (*Malassezia*) species are a group of yeast-like fungi that colonize the human skin. Questionably, these lipophilic yeasts have been incriminated in the pathogenesis of seborrheic dermatitis in normal hosts and in those with AIDS. At The Mount Sinai Hospital, Groisser, Bottone, and Lebwohl (21b) studied the association of *Pityrosporum orbiculare* in seborrheic dermatitis in 10 patients with AIDS. Based on a quantitative correlation between numbers of yeast cells of *P. orbiculare* adherent to keratinocytes and the clinical severity of seborrheic dermatitis in these patients, an association, if not etiologic role, for *Pityrosporum* was strongly suggested in seborrheic dermatitis in patients with AIDS. The association was further strengthened by the good clinical response to topical ketoconazole in two treated patients.

Campylobacter-like organisms (CLO) have been recovered from homosexuals with enteritis and/or proctitis (22). These organisms, termed "CLO," were genetically and phenotypically distinct from previously described *Campylobacter* species due to their sensitivity to nalidixic acid and cephalothin, failure to grow at both 25°C and 42°C and unusual odor in culture. Growth of *Campylobacter*-like organisms at 37°C is very slow; pinpoint colonies appear after 48 hr incubation. It is tempting to speculate that similar types of organisms will be found in homosexual patients with AIDS, since they constitute a large proportion of those afflicted with AIDS.

Vigilance in Detecting Multiple Agents. The list of agents associated with AIDS seems limitless and at present is only restricted by our ability to detect such microbial pathogens. A recent study (23) describes noncultivatible bacillary forms demonstrated by electron microscopy and histochemistry in subcutaneous nodules of an AIDS victim. This subcutaneous infection responded to antimicrobial therapy although a microorganism was never cultured *in vitro*. Observations such as these suggest an ever expanding list of unusual or variant microbial forms in those with AIDS.

The spectrum of the infectious and neoplastic complications found in the acquired immune deficiency syndrome remains unparalleled. Perhaps the most profound aspect is the marked frequency of multiple and concomitant opportunistic infections and neoplasms. Recently, Wormser commented on two AIDS patients who "between them had no fewer than nine different infections and two malignancies" (24). Thus it becomes of critical importance to microbiologists evaluating specimens from AIDS patients to be ever vigilant for the presence of multiple infectious agents. Our own experience has revealed *M. avium-intracellulare* and *C. neoformans* is blood specimens of patients with AIDS on several occasions (25), *M. tuberculosis* and *M. avium-intracellulare* in stool specimens (10), and cytomegalovirus and *Toxoplasma* in brain biopsies. The value of early

TABLE 2

Usefulness of Serologic Testing in Diagnosing Opportunistic Infections in Patients with AIDS.

Agent	Comment
Pneumocystis carinii	Detection of serum circulating antibody or antigen is neither sensitive nor specific in diagnosing *P. carinii* pneumonia.
Toxoplasma gondii	Rare fourfold or greater rise in antibody titer. Presumptive diagnosis by a single point titer of 1:1024 occurs in less than a third of patients with toxoplasma encephalitis. IgM Ab specific for toxoplasma rare.
Cryptosporidium	No available serologic test.
Mycobacterium avium-intracellulare	No available serologic test.
Aspergillus sp.	Antibody specific for antigen extracts of *A. flavus, A. fumigatus,* or *A. niger* not detectable in serum from AIDS patients.
Candida albicans	No significant differences in antibody titer between AIDS and non-AIDS populations.
Cryptococcus neoformans	Detection of circulating cryptococcal antigen in either the CSF or serum extremely sensitive and specific.
Cytomegalovirus	Approximately 50% of patients with proven CMV infection (culture or direct smear) show fourfold or greater rise or fall in titer; a single point titer may not be indicative of active infection. Specific IgM antibody may or may not be present.
Epstein-Barr virus	A presumptive serologic diagnosis of an active EBV infection may be demonstrated by a single point IgG titer (≥1:1024) to the viral capsid antigen or a fourfold or greater rise or drop in titer.
Herpes simplex virus	Fourfold or greater rise in titer may not be detectable in active HSV infections. A single elevated titer may be suggestive of a prior infection.
Varicella zoster virus	Difference in antibody titer between a homosexual AIDS population and a control group not significant.

recognition of an unsuspected pathogen may well lead to initiation of antimicrobial therapy prior to overt symptoms and at a time when the microbial burden is still manageable.

Serology

Serologic tests serve an important role in the primary diagnosis of HIV infection but are less useful in establishing the etiology of a particular opportunistic infection. These tests generally fall into two categories, namely those whose objective is to detect exposure to HIV (26), and those centered upon the diagnosis of infectious processes in these individuals (Table 2).

The usefulness of serologic tests in the diagnosis of opportunistic infections in patients with AIDS has been limited. This failure is in part due to the inability of patients with AIDS to mount a significant immunologic response against many pathogens. Although these patients show polyclonal B cell activation, they have a decreased ability to mount a de novo antibody response to new microbial antigens (27). As a consequence, there are no useful serologic tests available for the diagnosis of *Pneumocystis carinii, Cryptosporidium, Mycobacterium avium-intracellulare,* or *Aspergillus* infections in patients with AIDS. In these instances the definitive diagnosis is dependent upon in vitro cultivation of the agent in question or by demonstrating microscopically its presence in appropriate clinical material.

Among viral pathogens, the herpesvirus group (CMV, EBV, HSV) causes serious infections in patients with AIDS. With CMV, only approximately 50% of all individuals with primary infection documented by either culture or direct smear show a fourfold rise in antibody titers. Serum antibody titers to CMV do not differ significantly in homosexuals with or without AIDS, suggesting that a single titer is of little diagnostic or prognostic value. In contrast, individuals with AIDS have higher mean titers to the viral capsid antigen (VCA) of EBV than matched controls. Presumptive serologic evidence of active EBV infection (not mononucleosis) may be demonstrated by a single IgG antibody titer to VCA of 1:1024 or greater. With HSV, serology is minimally helpful; fourfold rises in complement fixation titers are detected in less than 30% of all documented infections in patients with AIDS.

Among parasitic infections, diagnosis of *Toxoplasma* encephalitis in patients with AIDS is difficult since it is rare to demonstrate fourfold rises in antibody titer. Presumptive diagnosis by a single point titer (immunofluorescence, Sabin-Feldman dye test) of 1:1024 occurs in less than one-third of all patients with encephalitis. Indeed, in our experience with several patients with multiple toxoplasmic brain abscesses, serum antibody titers ranged from 1:32 to only 1:128. The presence of IgM Ab specific for *Toxoplasma* is also rare in these patients.

Critical Need to Diagnose Treatable Infections. It is clear that as various treatment modalities against the human immune deficiency virus become available that may extend the life span of AIDS victims, the need to diagnose potentially treatable infections rapidly in this patient population is critical. Thus, because of the overlapping clinical presentations of the microbial pathogens afflicting patients with AIDS, the clinician must not be lulled into complacency by assuming that a radiologic finding of an interstitial pneumonia must be due to *Pneunocystis carinii.* Our own experience has shown that primary cryptococcal pneumonia (28), as well as pneumonia due to *Legionella* species (29), may also render such a radiologic pattern.

Concordant with the above, a high index of suspicion for an incipient immune deficiency state may also be microbiologically triggered. Thus, harbingers such as unexplained and/or recurrent salmonella (or even shigella) bacteremia in a previously healthy individual, or the isolation of *Mycobacterium avium-intracellulare* or (more recently) *M. tuberculosis,* may actually predate other more definitive manifestations of AIDS. In our hands, the observance of poorly encapsulated *C. neoformans* in the cerebrospinal fluid of a patient always begs the question of AIDS. It is such microbiologic subtleties, when finely tuned, that bring the clinician a firmer base for defining a therapeutic regimen against the spectrum of disease induced by human immune deficiency virus.

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Increased Incidence of Malignant Lymphoma in AIDS:

A Comparison of Risk Groups and Possible Etiologic Factors

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Abstract

The incidence of malignant lymphoma in AIDS patients at two New York City hospitals from 1981 to 1986 was compared with an age- and sex-matched population. The overall incidence of lymphoma in AIDS patients was 3.9% per year, representing a 194-fold increase over an age- and sex-matched population ($p < 0.001$). Most of this increased incidence was due to an increase in non-Hodgkin's lymphoma; however, a smaller but significant increase in Hodgkin's disease was also noted. The role of a number of possible risk factors for lymphoma, including AIDS risk group, simultaneous Kaposi's sarcoma, antibody titers to CMV, antibody titers to EBV, and T4/T8 ratio were also examined. The incidence of non-Hodgkin's lymphoma was found to be four times greater in homosexuals than in other AIDS risk groups ($p < 0.025$). EBV titers were significantly higher in AIDS patients with lymphoma than in other AIDS patients ($p < 0.05$). No differences in CMV titers, incidence of Kaposi's sarcoma, or T4/T8 ratios were observed. These studies confirm the markedly elevated incidence of non-Hodgkin's lymphoma in AIDS patients and suggest an etiologic role of EBV infection in the development of lymphoma.

Malignant lymphoreticular neoplasms occur with an increased frequency in hosts with inherited or acquired deficiencies of cellular immunity (1). More recently, an increase in the frequency of high-grade non-Hodgkin's lymphoma (NHL) and Hodgkin's disease has been reported in patients with the acquired immune deficiency syndrome (AIDS) (2–10). Although the incidence of lymphoreticular malignancies is clearly increased in patients with AIDS, there have been few studies documenting the magnitude of increase or associated risk factors. Evidence supporting the association of AIDS and NHL has been sufficiently strong that the Centers for Disease Control (CDC) amended their definition of AIDS to include non-Hodgkin's lymphoma of high-grade B-cell type, in the presence of a positive serologic or virologic test for the human immunodeficiency virus (HIV) (11). The association between Hodgkin's disease and AIDS, however, has not been as well studied. Several reports have suggested that Hodgkin's disease does occur with increased frequency in AIDS patients (12–20); however, quantitative studies are lacking.

The factors for the development of lymphoma in the setting of AIDS remains rather poorly defined. Studies of both Hodgkin's and non-Hodgkin's lymphoma have included a heterogeneous population of persons with AIDS, AIDS-related complex (ARC), or generalized lymphadenopathy, and homosexual men (3–4, 21). Studies have tended to concentrate almost exclusively on homosexual men, and little is known about the incidence of lymphoma among other AIDS risk groups, including intravenous drug abusers (IVDA), hemophiliacs receiving factor VIII concentrate, transfusion recipients, prison

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inmates, and so on. Since Kaposi's sarcoma, another AIDS-associated neoplasm, is known to occur with much greater frequency in homosexual men than in the other AIDS risk groups (22), a comparison of risk groups with respect to the development of lymphoma in AIDS may be of value in understanding the pathogenesis of this neoplasm.

Risk factors for the development of lymphoma in AIDS have not been well characterized. Studies have implicated Epstein-Barr virus (EBV) in the development of non-Hodgkin's lymphoma, in both AIDS and non-AIDS settings (23–29). Cytomegalovirus (CMV) has been implicated in the development of Kaposi's sarcoma, also in both AIDS and non-AIDS settings (30), and the incidence of lymphoid neoplasms in non-AIDS patients with primary Kaposi's sarcoma is increased over the general population (31). CMV is also known to be immunosuppressive (32, 33) and may, therefore, predispose to the development of lymphoma. Epstein-Barr virus infection, cytomegalovirus infection, low T4/T8 ratios, and Kaposi's sarcoma may therefore be potential risk factors for the development of lymphoma in AIDS.

In the present study, we have examined (a) the risk of non-Hodgkin's lymphoma and Hodgkin's disease in a defined population of patients with AIDS, (b) the distribution of lymphoma amongst AIDS populations with different risk factors, and (c) the role of possible etiologic factors in the development of lymphoma, including Epstein-Barr virus infection, cytomegalovirus infection, degree of immunosuppression as evidenced by T4/T8 ratios, and concomitant Kaposi's sarcoma. The results are discussed with respect to possible pathogenetic mechanisms.

Methods

The study group included all patients with a diagnosis of AIDS seen at The Mount Sinai Hospital (MSH) and St. Vincent's Hospital (SVH) between January 1981 and June 1986; the total number of such patients was 743. The diagnosis of AIDS was based on the CDC criteria (34) and confirmed by retrospective chart review. All patients were classified in CDC groups IV C or D (11). Data was collected by retrospective chart review. All histologic diagnoses of lymphoma were reviewed and classified according to the Non-Hodgkin's Lymphoma Pathologic Classification Project (working formulation) (35). From this study group, the 31 patients identified as having a histologic diagnosis of lymphoma and meeting the CDC criteria for AIDS constituted the study group. In two, case records were not available for review, and these cases were excluded. A control group of 32 AIDS patients without lymphoma was selected using sequential chart number.

The cases of the 29 patients with AIDS and lymphoma (subject mean age, 38.2 years), and the 32 patients with AIDS alone (control mean age, 33.6 years) were analyzed. Twenty-seven of the 29 subjects, and all 32 controls, had chart-confirmed diagnoses of AIDS. Two of the subjects with Hodgkin's lymphomas who had diagnoses of AIDS were, on review, found not to meet the CDC criteria and were reclassified as ARC. All of the patients with lymphomas and AIDS were male; 3 of the control patients were female.

All charts were reviewed with regard to the following information: demographics, date of diagnosis of AIDS and risk group, date of diagnosis of lymphoma, histology, grade and state of tumor, the presence of extranodal involvement, and possible lymphoma risk factors, that is, concomitant KS, CMV, and EBV titers, and T4/T8 ratios.

To ensure compatibility of the study groups, the total number of AIDS cases, at both MSH and SVH, was determined over the past five years, and the frequency distribution for the different AIDS risk groups was also determined. To ensure generalizability, data were also obtained on risk group distribution in New York City over the past five years (courtesy of New York City Department of Health), and these data were compared with the study sample (Table 1).

The incidence rate of all lymphomas in AIDS patients was determined for the study interval. Separate incidence rates for NHL and Hodgkin's disease in AIDS were determined. The relative risk for the development of lymphoma between AIDS and age and sex matched non-AIDS groups was calculated. Incidence rates were compared by χ^2 analysis.

AIDS patients with lymphoma were compared to controls with respect to the existence of concomitant KS, CMV titers, EBV titers, and T4/T8 ratios, in a case control design. KS was diagnosed from biopsy material reviewed by pathologists at the collaborating institutions. Serum antibodies to CMV were measured by complement fixation or latex agglutination tests. Serum antibodies to Epstein-Barr viral capsid antigens were measured by indirect fluorescent antibody (IFA) technique. T4/T8 ratios were determined by immunofluorescence on peripheral blood. Statistical analyses were performed by χ^2 and Mann Whitney U, as appropriate. Although means for immunologic tests were generated, nonparametric tests were used for analyses.

Results

Lymphoma Histology. Of the 29 lymphomas observed, 24 (83%) were non-Hodgkin's lymphomas and 5 (17%) were Hodgkin's disease. In an analysis of lymphoma type according to AIDS risk group (categorized as homosexual/bisexual; intravenous drug abuser; homosexual/intravenous drug abuser; and other [sexual partner of prostitutes]), a greater-than-expected frequency of non-Hodgkin's lymphoma was seen in the homosexual/bisexual group (Table 2). Interestingly, a greater-than-expected frequency of Hodgkin's lymphoma was seen in the intravenous drug abuser and homosexual/intravenous drug abuser categories. Expected frequencies were too low for chi-square analysis.

The clinicopathologic features of the non-Hodgkin's lymphomas (Tables 3,4) included 58.3% high-grade, 29.2% intermediate-grade, no low-grade, and 12.5% unclassified tumors. Stage IV presentation was by far the most common (79.2%). Extranodal involvement occurred in all but one case of non-Hodgkin's lymphoma (96%), involvement of the central nervous system, bone marrow, skin/mucosa, and gut being the most common.

Incidence of Lymphoma. The average incidence of malignant lymphoma in the study group was 3.9% per year. The yearly incidences of non-Hodgkin's lymphoma and Hodgkin's disease in the study years, 1981 to 1986, were 3.2% and 0.7% respectively. These rates were compared with the age-adjusted incidence rates of lymphoma in New York City. The specific reference group was selected conservatively: that male age group, within two standard deviations of the mean age of our subjects, that yielded the greatest number of lymphomas over the time period 1981–1984. For all lymphoreticular malignancies, the group aged 45–49 years yielded an average expected yearly incidence of 0.02%. The relative risk of developing any lymphoma in AIDS is 194 times greater (χ^2 [1] = 5,566, $p < 0.001$). Using New York City reference data for non-Hodgkin's lymphoma, the group aged 40–44 years yielded an average expected yearly incidence of 0.006%, and for Hodgkin's disease, the group aged 25–29 years yielded an expected yearly incidence of 0.006%. In comparison to the reference data, the relative risk of developing non-Hodgkin's lymphoma in AIDS is 516 (χ^2 [1] = 12,339, $p < 0.001$), and the relative risk of Hodgkin's disease was 72 (χ^2 [1] = 210, $p < 0.001$).

The incidence of non-Hodgkin's lymphoma by AIDS risk group was also compared. For the purposes of this analysis, AIDS risk groups were categorized as homosexual/bisexual versus all other risk groups—intravenous drug abusers, homosexual intravenous drug abusers, and other. The incidence of non-Hodgkin's lymphoma was found to be four times greater in the homosexual/bisexual group than in the combined category (χ^2 [1] = 5.72, $p < 0.025$).

Lymphoma-Associated Risk Factors. Patients with AIDS and NHL were compared to those with AIDS alone for the simultaneous occurrence of KS (Table 5). Controls were matched to subjects with respect to AIDS risk group to control for the increased incidence of KS among homosexuals. Although the incidence of Kaposi's sarcoma was twice as great in AIDS patients with lymphoma than in those without, the difference was not significant (χ^2 [1] = 2.48 NS).

Patients with AIDS and NHL were compared to those with AIDS alone for EBV and CMV titers. All titers for cytomegalovirus and Epstein-Barr virus were drawn within six months preceding or concurrent with the diagnosis of lymphoma. CMV titers were available on 13 subjects and 9 controls. Subject and control values were not significantly different. EBV titers to viral capsid antigen (VCA) were available for 10 subjects and 5 controls. Subject and control values were significantly different ($p < 0.05$ U = 6).

Patients with AIDS and NHL were compared to those with AIDS alone for T4/T8 ratios. Nine subjects and seven controls had T4/T8 ratios recorded. Mean values were .34 and .37, respectively. Values for subjects were not significantly different from values for controls. Hodgkin's lymphomas numbered too few to perform a similar analysis for these risk factors.

Discussion

The clinicopathologic features of the non-Hodgkin's lymphomas in our study conform to findings of other investigators (2–10). The distribution of histology, 58% high grade and 29% intermediate grade, closely parallels the study by Ziegler et al. (2). The findings of advanced stage at presentation, and a marked propensity for extranodal involvement, also support the findings of other investigators.

The incidence of lymphoma of 3.9% per year in patients with AIDS confirms the impression that the incidence of lymphoid malignancies is dramatically increased in AIDS. The risk of developing lymphoma in patients with AIDS is almost 200-fold greater than that of the age- and sex-matched population. This increased incidence is due mostly to an increase in the frequency of non-Hodgkin's lymphoma (3.6%). However, a smaller but significant increase in the number of Hodgkin's lymphomas is also demonstrated (0.7%).

Our study shows that homosexuals and bisexuals have a fourfold greater risk of developing non-Hodgkin's lymphoma than people in the other AIDS risk groups combined. Non-Hodgkin's lymphoma, like Kaposi's sarcoma, appears to occur with greater frequency in homosexuals than in other AIDS risk groups.

Studies have linked Kaposi's sarcoma (KS) with the development of lymphoid malignancies in patients without AIDS (31). Cytomegalovirus has been implicated as the etiologic cause of classical KS in some studies (36–37), as well as in the epidemic form of KS seen in AIDS patients (36). CMV infection is common in homosexuals. Ninety-four percent of 139 homosexual men were found to be antibody positive to CMV, compared to only 54% of 70 heterosexual men (38). Intravenous drug abusers, surprisingly, have been shown to have rates of CMV infection similar to that of the general population (39). The data are consistent with a role of CMV in the genesis of KS in AIDS, since the incidence of KS in homosexual or bisexual men with AIDS is over 40% (36), whereas the incidence of KS in intravenous drug abusers with AIDS is only 4–5% (40).

AIDS patients with KS do not appear to be at greater risk for the development of lymphoma, since no significant difference could be found between subjects and controls in the occurrence of KS. In addition, no difference was found between subjects and controls in the levels of CMV titers. This data suggests that CMV is not involved in the pathogenesis of NHL in AIDS.

T4/T8 ratios were examined to assess whether the degree of immunodysregulation in AIDS correlated with the development of lymphoma. Subjects and controls did not differ in this parameter; however, the T4/T8 ratio is at best only a crude indicator of immunologic function.

The role of EBV in the development of Burkitt's and other non-Hodgkin's lymphomas in patients without AIDS has been strongly suggested (1, 23, 24). In AIDS patients with lymphoma, Epstein-Barr nuclear antigen and EBV genomes have been detected in Burkitt's-like lymphomas (8, 25), and in a diffuse, large-cell lymphoma (26). Serologic studies on homosexual men have dem-

TABLE 1

Demographics and Frequency Distribution of AIDS Risk Groups: A Comparison of the Study Group and the NYC AIDS Population

	Controls n = 32	Study group n = 743	NYC n = 8,569
Mean age	33.6	37.5	36.8
Range, age	<1–51	<1–68	N/A
Homosexual/ bisexual men	56%	64%	58%
IVDA	19%	23%	30%
Homosexual IVDA	12.5%	4%	5%
Other	12.5%	9%	7%

IVDA, Intravenous drug abuser; Other, sexual partner of prostitutes.

TABLE 2

Lymphoma Type by AIDS Risk Group

	Homo/ Bi	IVDA	Homo IVDA	Other	Total
Non-Hodgkin's lymphoma	21 (18.7)	1 (2.6)	1 (1.7)	1 (1.0)	24 83%
Hodgkin's lymphoma	2 (2.3)	2 (.33)	1 (.21)	0 (.11)	5 17%
Total	23 79%	3 10%	2 7%	1 3%	29

Homo/Bi, homosexual or bisexual; IVDA, intravenous drug abuser; Homo + IVDA, homosexual intravenous drug abuser; Other, sexual partner of prostitutes.

Numbers in parentheses are expected cases.

TABLE 3

Histologic Subtype and Staging of 24 Cases of Non-Hodgkin's Lymphoma in Patients with AIDS

	No. of pts	%
Histologic subtype of lymphoma		
High-grade		
Large cell, immunoblastic	11	45.8
Small, non-cleaved cell (Burkitt's)	3	12.5
Total	14	58.3
Intermediate-grade		
Diffuse, large cell	6	25
Diffuse, mixed large and small cell	1	4.2
Total	7	29.2
Low-grade	0	0
Unclassified	3	12.5
Staging		
Stage IV		79.2%
Stage II		4.2%
Stage I		8.3%
Unstaged		8.3%

onstrated 99.7% EBV-seropositivity, compared to 91% in heterosexual male controls (27). A twofold increase in the rate of viral reactivity in homosexuals with AIDS and persistent generalized lymphadenopathy, as compared to heterosexual male controls, has been reported (27).

Our study demonstrated that AIDS patients with NHL have significantly higher EBV titers than AIDS patients without lymphoma. These results support previous data that EBV may be a major etiologic agent in the development of NHL in AIDS. That homosexual males have been shown to have higher rates of both prior and reactivated EBV infection than heterosexual males is consistent with our observations that homosexual men are at higher risk for the development of NHL than members of other AIDS risk groups.

The possible role of EBV in the development of non-Hodgkin's lymphoma in AIDS patients has been suggested by a number of studies. Following EBV-induced infectious mononucleosis in the normal host, a small number of circulating B-cells remain chronically infected (41–43). The proliferation of these cells is inhibited by regulatory T-cells (44, 45). In EBV-seropositive blood from AIDS patients, there is a decrease in this normal T-cell suppression so that a greater number of circulating EBV-infected B-cells are capable of spontaneous proliferation in vitro than in normal controls (29). This may offer an explanation for the presence of abnormally high numbers of EBV-infected B-cells in the blood of patients with AIDS, a condition believed to be important in the development of B-cell lymphoma in a host with defective cellular immunity (29).

T-cell immunodeficiency predisposes to a variety of malignancies (3, 28). The proposed pathogenesis of a B-cell lymphoma in patients with AIDS and EBV exposure may require multiple steps. First, EBV acts as a B-cell mitogen, initiating a polyclonal B-cell proliferation. Second, the defect in cellular immunity allows a sustained polyclonal B-cell proliferation which can persist indefinitely (1, 3). Third, because of a larger B-cell population at risk, these rapidly proliferating cells are at enhanced risk of acquiring cytogenetic aberrations, such as translocations, which could lead to oncogene activation. This transformed cell would have a growth advantage, and from a pool of proliferating immunocytes, a monoclonal lymphoma could result.

EBV, then, is not necessarily directly oncogenic but may, by acting as a B-cell mitogen, create an environment suitable for the critical gene rearrangements that lead to the oncogenic event (1, 3). Lending support to this hypothesis is a study by Meter et al. (47) of serial pathologic sections of lymph nodes from homosexual patients with generalized lymphadenopathy. In some of the cases, a progression from polyclonal B-cell proliferation to lymphoma was seen.

TABLE 4

Extranodal Sites of Involvement in 24 Cases of non-Hodgkin's Lymphoma in Patients with AIDS

Site	No. of pts	Site	No. of pts
CNS		Pharynx	1
Primary brain	3	Lung	4
Metastatic to brain	2		
Spinal cord	1	Gastric	3
Total	6	Diffuse abdomen	3
Bone marrow	4	Small intestine	2
Skin/mucosa			
Intraoral	1		
Neck	2		
Cutaneous nodules	1		
Thigh	1		
Anorectal	3		
Total	8		

TABLE 5

Non-Hodgkin's Lymphoma: Possible Risk Factors

	Subjects	Controls
Kaposi's sarcoma	52% n = 21	28% n = 21
Mean CMV titers	1:119 n = 13 Range = 1:4–1:640	1:139 n = 9 Range = 1:8–1:640
Mean EBV titers (VCA)	1:4, 472* n = 10 Range = 1:80–1:40,000	1:122 n = 5 Range = 1:8–1:320
Mean T4/T8 ratio	.34 n = 9 Range = .06–.82	.37 n = 7 Range = .07–1.23

* Subjects significantly different from controls ($p < .05$) by Mann Whitney.

U nonparametric analysis.

All other comparisons are NS.

HIV itself may also play a more direct pathogenic role in the development of B-cell neoplasia. Evidence has been presented which suggests that HIV may be able to directly infect and propagate in B-lymphocytes (7). Prior EBV infection of these B-cells appears to be necessary in order to predispose them to retroviral infection (7, 12).

Antigen activation of lymphocytes may also play a role. Repeated sexual involvement with multiple partners in homosexuals exposes the host not only to EBV but a wide variety of agents to which neither the general population nor intravenous drug abusers are exposed. These include various types and strains of viruses, parasites, bacteria, and allogeneic sperm, all of which could potentially stimulate B-cell proliferation. Immunostimulation in a homosexual male with a depressed cellular immune system due to AIDS is a possible setting for B-cell proliferation and the development of B-cell lymphoma. These agents may be responsible for the finding that homosexuals with AIDS are more susceptible to the development of lymphoma than the other risk groups.

Lastly, a word about Hodgkin's disease. The occurrence of Hodgkin's disease in an immunocompromised host is not unique to AIDS. Patients with primary immune deficiency syndromes are also known to develop Hodgkin's disease with an increased incidence, and with an unfavorable histologic subtype and aggressive clinical course (13). Although in our sample of AIDS patients the number of Hodgkin's lymphomas was too small for an extensive analysis, a significant increase in the incidence of these lymphomas was noted. Interestingly, these lymphomas appeared to occur with greater than expected frequency in those patients with a history of intravenous drug abuse. Case reports of Hodgkin's disease in AIDS have described its occurrence in homosexual men (12–20); however, one quarter of these patients were IVDAs as well, and for most of the others, no social history was presented. Therefore, the possibility exists that a far greater number of these patients were IVDAs than was reported. Greater attention to risk group breakdown is clearly needed to accurately resolve this matter.

It is unclear why these lymphomas may occur more frequently in IVDAs. One possibility has to do with the pharmacology of the drugs used by IVDAs. Opiates can bind to T-cells and thereby depress cellular immunity (27). These pharmacologic agents, by affecting the level and type of immunosuppression, may therefore play a role in the pathogenesis of Hodgkin's lymphoma in AIDS.

In summary, the incidence of lymphoreticular malignancies, including non-Hodgkin's lymphoma and to a lesser extent Hodgkin's disease, is greatly increased in AIDS. EBV and possibly other factors may play a major role in the development of these lymphomas.

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Leucovorin as a Clinical Potentiator of 5-Fluorouracil Toxicity and Anticancer Efficacy

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Abstract

Several 5-fluorouracil (FUra) regimens (infusion at 231 × 10^{-6} M/kg/day [30 mg/kg] × 5 given to 10 patients, bolus day 1 at 115–173 × 10^{-6} M/kg [15–22.5 mg/kg] every 3 weeks given to 25 patients, and bolus day 1 and 2 at 115–135 × 10^{-6} M/kg/day [15–17.5 mg/kg] given to 9 patients) produced more severe and life-threatening toxicity than anticipated, when the regimen was given in combination with small, 25 × 10^{-6} M/m^2 [15 mg/m^2] doses of leucovorin (LV) three times a day with infusion or once daily with the bolus regimens. The doses of FUra alone are usually far less toxic. The patients with advanced cancer of the colon or rectum experienced no similar level of toxicity with earlier, sometimes more intensive, FUra regimens. Full patient safeguards are required in developing any dosage of LV as a modulator of FUra. Several instances of tumor regression were observed in patients with colonic, pancreatic, and bladder cancer already clinically refractory to FUra. The infusion regimen produced 2 partial responses; the day 1 regimen produced 1 partial and 7 minor responses; and the day 1,2 regimen produced 1 partial and 2 minor responses.

Low doses of LV in combination with FUra produce multiple biologic effects. It is not possible to provide a definitive examination of the effect of dose on response or survival because of the heterogeneity of the patients and the small sample sizes. One cannot assume the safety of combining even small pharmacologic doses of an otherwise harmless agent such as LV with cytotoxic drugs.

Reduced folates are cofactors for the 5-fluorodeoxyuridine-monophosphate (FdUMP) thymidylate synthetase reaction (1, 2). Leucovorin (LV) is a potentiator and biochemical modulator of 5-fluorouracil (FUra) cytotoxicity in vitro (2–4). Low concentrations of LV appear to modulate FUra in some of these experiments (2–4).

This report describes the original clinical evidence that LV is a potentiator of FUra (5). It includes the observation that small doses of LV may markedly increase the toxicity of FUra, so that conventional doses of FUra sometimes produce unacceptable toxicity when given with LV. This toxicity has not yet received the emphasis it deserves in planning "safe" clinical treatments with LV and FUra.

Some patients with progression of disease during treatment with FUra have had regression of tumors when LV was added to the previously unsuccessful FUra regimen, even if FUra was employed in the same schedule but in smaller total dosage than before. Similar responses have now been reported by additional investigators employing larger doses of LV (6, 7).

Patients, Material, and Methods

Infusion Regimen. Ten patients were entered in Group 1. All had prior therapy with 2 or

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more courses of FUra infusion, as part of HexMF (14 days of hexamethylmelamine and 1 day of mitomycin-C at 30 × 10^{-6} M/m^2 [10 mg/m^2] every 4–5 weeks), identical in dosage and schedule to that in the LV-FUra regimen given before (8, 9). All patients had progression of disease during treatment with HexMF. Seven had appearance of new sites of metastatic tumor or >25% progression of measurable sites of tumor. Three had both diminished performance status and worsening blood tests due to disease but no measurable tumor. All had carcinoma of the colon. Five were ≤60 years of age and six were men. Patients were again treated with an identical constant rate of a FUra infusion of 231 × 10^{-6} M/kg/day [30 mg/kg], (1–5 days as tolerated). The endpoint of the infusion was 5 days or the first evidence of epithelial toxicity or blood count depression, WBC ≤4 × 10^9/L or platelets ≤100 × 10^9/L. In addition, patients were treated with LV 25 × 10^{-6} M/m [15 mg/m^2] as a 10 minute "piggyback" infusion once every 8 hours without interrupting the rate of the FUra infusion. LV was started on day 2 of the FUra infusion and a maximum of 9 doses were given during the FUra infusion.

Bolus Regimen. Thirty-four patients were entered in Group 2: 76% had prior chemotherapy with subsequent progression of disease. Diagnoses included carcinomas of the colon, 23; rectum, 3; pancreas, 2; stomach, 1; esophagus, 1; bladder, 1; breast, 1; melanoma, 1; and unknown site, 1. Age, with a cut off at 60 years, and sex were distributed evenly. The patients' performance status (PS) was 10, PS-0; 12, PS-1; 4, PS-2; 5, PS-3; 1, PS-4; and 2 unspecified. Patients were treated with FUra either as a single (D1) bolus (25 patients) or on two consecutive days (D1, 2) every three weeks (9 patients). One hour before each FUra bolus, the patient was treated with 25 × 10^{-6} M/m^2 [15 mg/m^2] of LV as a 10 minute infusion. Patients were assigned to D1 or D1 & 2 treatment in a non-random fashion. Doses of FUra were escalated in successive cohorts of patients.

Treatment was repeated every 29 days in Group 1 (infusion) and 22 days in Group 2 (bolus) provided the WBC >4 × 10^9/L and platelets >100 × 10^9/L. The dosage of FUra was decreased 25% for a nadir WBC <1 × 10^9/L or platelets <75 × 10^9/L or grade 3 mucositis, and 50% for a nadir WBC <0.5 × 10^9/L or platelets <50 × 10^9/L or for infection or bleeding due to the preceding treatment with LV & FUra. LV doses were not changed.

Eligibility requirements included: proven cancer, incurable with surgery or radiotherapy; performance status 0–3; and stable medical status and an anticipated survival of at least 4 weeks. Contraindications included active bleeding, infection or bowel or urinary tract obstructions, abnormal Cancer Acute Leukemia Group B grade 2 major organ function, abnormal grade 1 bilirubin, or anticipated requirement for palliative radiotherapy or surgery. Patients with prior therapy were eligible provided they had no radiation within 4 weeks and had recovered from prior chemotherapy or radiotherapy (WBC >4 × 10^9/L and platelets >100 × 10^9/L). All patients gave informed consent in accord with institutional requirements.

Toxicity was evaluated in standard fashion with complete blood counts every week, full chemistries every 3–4 weeks, review of systems and physical examination every 3–4 weeks, and additional tests as clinically indicated. Full supportive and symptomatic care were employed as required. Toxicities were defined as follows: Grade 4: WBC <1 × 10^9/L, platelets <25 × 10^9/L, or stomatitis requiring hospitalization. Grade 3: WBC 1 × 10^9/L – 2 × 10^9/L, platelets 25 × 10^9/L – <50 × 10^9/L, or stomatitis, unable to eat. Grade 2: WBC 2 × 10^9/L – <3 × 10^9/L, platelets 50 × 10^9/L – <90 × 10^9/L, or stomatitis, ulcers, but able to eat.

Responses were defined as follows: complete response (CR), complete disappearance of all tumors by physical examination and x-ray; partial response (PR), >50% decrease in the product of perpendicular tumor diameters or >50% decrease in the span of the liver below the costal margin, provided the span was initially >5 cm on quiet respiration; minor responses (MR), >25% decrease in the product of perpendicular tumor diameters, as determined by physical examination, sonogram or CAT scan or a decrease in actively increasing pathological fluid with no other intervention for >3 wks, or >50% decrease in carcinoembryonic antigen, initially five times greater than the normal or >50% decrease in abnormal chemistries initially 4× greater than the normal; progressive disease (PD), >25% increase in the product of perpendicular diameters, appearance of any new tumor or pathological fluid, or doubling of any abnormal laboratory test due to disease, or 1 step deterioration in performance status for >3 wks; stable disease (SD), none of the above characteristics of response or progression during 3 cycles of chemotherapy.

Progression-free interval and survival were determined in standard fashion from the first day of actual treatment. There were no exclusions of patients.

Results

Toxicity: Infusion Regimen. Ten patients were treated with the FUra infusion plus LV. Findings include 1 grade 4 (life-threatening) and 2 grade 3 (severe) hematologic toxicities. The overall cumulative incidence of grade ≥ 2, moderate or worse, toxicities were: 50% thrombocytopenia; 20% leukopenia; and 60% mucositis. The duration of the FUra infusion was shorter than in previous infusions without LV median 88 hours, range 72–94 hours, vs median 106 hours, range 96–120 hours ($p < .02$). The identical FUra infusion, without LV, had been adjusted during the course of earlier therapy to produce consistent but only mild toxicity, and had produced a less than 10% incidence of either mild or worse hematologic toxicity and neither moderate nor worse grade ≥ 2 epithelial toxicity after initial dosage adjustments (10, 11, 12).

Toxicity: Bolus Regimen (Day 1). The single day bolus schedule produced grade 2 toxicity in 5 of 6 patients treated at 154×10^{-6} M/kg [20 mg/kg] and 5 grade 2, 2 grade 3, and 1 grade 4 toxicity in 8 of 13 patients treated at 173×10^{-6} M/kg [22.5 mg/kg]. The 173×10^{-6} M/kg [22.5 mg/kg] dosage produced a 44% risk of Grade 2 toxicity and a 22% risk of Grade 3 or 4 toxicity for patients with prior therapy (Table 1). The grade 3 and 4 toxicities were instances of granulocytopenia. The nadirs occurred 14–21 days after treatment. Mucositis and conjunctivitis which appeared 4–8 days after treatment were rare, only mild or moderate in severity, and of short duration.

Toxicity: Day 1, 2 Bolus Regimen. The D1, 2 bolus schedule produced 1 grade 1 and 1 grade 3 toxicity in 3 patients treated at 115×10^{-6} M/kg [15 mg/kg] (total 231×10^{-6} M/kg [30 mg/kg]). It produced 1 grade 1, 1 grade 2 and 2 grade 4 (life-threatening) toxicities in 4 patients treated at 135×10^{-6} M/kg [17.5 mg/kg] (total 269×10^{-6} M/kg [35 mg/kg]) (Table 1).

Therapeutic Effect

The LV and FUra infusion produced 2 objective partial responses and 3 stable disease for ≥ 3 months in 7 patients with measurable disease. Two patients had tumors with early progression. Three remaining patients with non-measurable disease did not progress for ≥ 3 months.

The overall response rate, including minor responses, for the two bolus regimens was 32% with a 95% confidence limit of 16–48%. This included 2 PR and 9 MR as shown in Table 2.

The D1 schedule produced 1 partial response; 7 (28%) MR; 5 (20%) SD for ≥ 3 months; and 11 (44%) PD in ≤ 3 months. A response was observed in a patient with cancer of the colon and minor responses in patients with cancer of the colon, rectum and pancreas (Table 2).

The D1–2 regimen produced 1 (11%) PR; 2 (22%) MR; 3 (33%) SD; and 2 (22%) PD. The partial responder had cancer of the rectum and the minor responders had cancer of the colon and bladder (Table 2). Individual responses are described in Table 3. One of the minor responses on second review meets partial response criteria.

The maximum follow-up for these 34 bolus LV plus FUra patients was one year. Median survival time was seven months. It is not possible to provide a definitive examination of the effect of dose on response or survival because of the heter-

TABLE 1

LV and FUra Bolus: Dosage, Schedule and Toxicity

			Maximum toxicity									
Daily dosage FUra	Pts. no.		None		Mild		Moderate		Severe		Life threatening	
	D1	D1-2	D1	D1-2	D1	D1-2	D1	D1-2	D1	D1-2	D1	D1-2
115	4^1	3	2^1	1	0	1	1	—	1	1	0	—
135	2	4^2	0	—	1	1	1	1	0	—	0	2^2
154	6^1	2	1	—	0	—	5^1	2	0	—	0	—
173	13^4	—	3^1	—	2^1	—	5^1	—	2^1	—	1	—
Total	25^6	9^2	6^2	1	3^1	2	12^2	3	3^1	1	1	2^2

Superscript: number treated as primary therapy.
FUra dosages are in SI units.

TABLE 2
Response to LV and FUra Bolus

	Schedules			
	Day 1		Day 1 & 2	
Response	No.	(%)	No.	(%)
Partial	1^{1}	(4)	1^{1}	(11)
Minor	7^{2}	(28)	2	(22)
Stable	5^{1}	(20)	3	(33)
Progression	11^{2}	(44)	2^{1}	(22)
Not evaluable	1	(4)	1	(11)
TOTAL	25^{6}	100	9^{2}	100

PR + MR 32% (95% CL: 16–48%).
Superscript: no. treated as primary therapy.

TABLE 3
Response to LV and FUra Bolus

Tumor	Prior Rx	FUra Dose (mg/kg) & schedule		Response (Decreased)	
Bladder	Yes	115	D1, 2	Lymph node	45%
				Alk phos	50%
				Pain	
Colon	Yes	115	D1, 2	Liver size	35%
				Alk phos	50%
Rectum	No	135	D1, 2	Node	50%
Colon	No	154	D1	Abd Mass	>25%
Rectum	No	115	D1	Lymph node	60%
				Lymph edema	60%
				Alk Phos	50%
Colon	No	173	D1	Chest X-ray	70%
Colon	Yes	173	D1	Alk Phos,	
				Bilirubin	70%
				Pain	
Pancreas	Yes	154	D1	Sonogram	>25%
				Alk phos	50%
Colon	Yes	173	D1	Liver size	>25%
				Pain	
Colon	Yes	173	D1	Liver size	40%
Colon	No	173	D1	Liver scan	>25%

FUra dosages are in SI units.

ogeneity of the patients and the small sample sizes.

Discussion

LV may produce treatment-limiting toxicity significantly in excess of that previously observed when the identical FUra infusion had been combined with Mitomycin-C and hexamethylmelamine for the same patients (8, 9). There was substantial hematological toxicity and the duration of the infusion was shortened due to earlier appearance of epithelial toxicity, although the infusion (without LV) had already been adjusted to produce a safe biologic endpoint of minimal mucositis. The infusion without LV and with additional cytotoxic drugs rarely produces any severe hematological toxicity (10, 11, 12).

The level of toxicity probably cannot be explained as due to debilitation caused by disease progression. Some, in group 2, had toxicity in spite of no prior therapy. The FUra infusion has been used as a secondary regimen without similar severe toxicity (8, 9).

As little as 42×10^{-6} M [25 mg] of LV may increase the potency of a bolus FUra regimen. It is unlikely that this is due to the dosage of FUra. Conventional doses of FUra were given to the majority of these patients especially patients given the most toxic of the three regimens, the D1–2 schedule. The largest bolus doses were only 25% greater than conventional doses. Less than half of the usual total loading course of FUra produced dose-limiting severe or life-threatening toxicity.

LV and FUra may produce objective regression of tumors already refractory to FUra (5–7). The biologic effect associated with these low 42×10^{-6} M [25 mg] doses of LV led to further studies of low-dose LV and intermittent FUra (13, 14). This line of investigation appears to lead to regimens which increase the frequency and quality of response to FUra in primary chemotherapy trials (6, 7) as well as new, more efficient, less time consuming, treatment schedules for FUra (13, 14). A single dose of LV daily is apparently less toxic, and probably less efficacious, than the three times a day LV schedule (15, 16). Biochemical modulation of FUra by LV, increases the toxicity of FUra, even at the low dosages of FUra employed in some of these regimens (6, 7).

These combined results provided the first demonstration of both a toxic and a therapeutic interaction between a vitamin and a cytotoxic drug in humans, other than the conventional application of LV (5). This interaction affects both normal and tumor tissue. The observed effect on normal tissue demands caution in designing trials and clinical applications. Published trials continue to fail to emphasize the necessary safety precautions while emphasizing applicability as initial and second-line treatment. Toxicity can probably now be largely prevented with careful dosage selection and adjustment, however, the potential risk must first be appreciated (17). Both primary and secondary therapy carry risk, but it may be greatest with the latter, especially when used without the safety provided by study mechanisms. One cannot assume the safety of combining even small pharmacologic doses of an otherwise harmless agent such as LV with cytotoxic drugs.

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Addendum. A recent interim review of a Gastrointestinal Tumor Study Group trial testing high-dose weekly treatment with LV-FUra as initial treatment found a near 10% rate of fatal side effects, many with an early gastrointestinal component, for patients older than 65 years of age. This occurred in spite of warnings of potential hazards to the elderly and an extensive list of precautions and contraindications based on earlier experience (17, 18). This serves to extend the scope of the warning regarding the potential risks of LV-FUra and has led some collaborative groups to initial use of 20% smaller doses of FUra and to temporarily stop therapy at the very first sign of distal gastrointestinal side effects. Nevertheless, with precautions, LV-FUra appears to provide safe treatment and improved rates of response compared to FUra alone.

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The Problem of Diagnosing Bacterial Pneumonia in Patients with Chronic Bronchitis

Bacteria in Sputum and Bronchial Washings from Patients with Chronic Bronchitis Are Antibody Coated

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Abstract

Bronchial wash samples and sputum were obtained from 25 patients with stable chronic bronchitis and evaluated by immunofluorescence techniques to determine whether bacteria in the samples were coated with antibodies. The purpose of the study was to define the potential usefulness of the procedure in diagnosing bacterial pneumonia in patients with chronic bronchitis. We found that 18 of 25 bronchial wash samples and 20 of 21 sputum samples contained more than five bacteria per oil immersion field (× 1,250) that were coated with IgG, IgA, or IgM. The results indicate that determination of antibody coating of bacteria in patients with chronic bronchitis offers little potential value in diagnosing bacterial pneumonia in these patients.

It is difficult to precisely diagnose bacterial pneumonia in the absence of positive blood cultures or positive cultures of pleural or lung fluids. Although Gram stain and culture of expectorated sputum are frequently used as diagnostic maneuvers, neither procedure accurately differentiates colonization of the oropharynx and upper airway from potentially significant lower-respiratory-tract infection (1, 2). Because of the need for more specific diagnostic tests, other methods have been developed, including quantitative sputum cultures, transtracheal aspiration, percutaneous lung aspiration, coagglutination, counterimmunoelectrophoresis, and the use of a telescoping plugged catheter inserted through a fiberoptic bronchoscope (3–5). A single report has appeared indicating that the quantitation of antibody-coated bacteria in bronchial secretions has diagnostic value in detecting bacterial pneumonia (6). In the study the investigators found that antibody-coated bacteria were detectable in bronchial brush samples during 24 of 33 episodes of lower-respiratory-tract infections in 31 patients. In contrast, antibody-coated bacteria were found in bronchial brush samples in only 1 of 60 control patients.

It is particularly difficult to diagnose bacterial pneumonia in patients with chronic bronchitis, because the airways of patients with chronic bronchitis are colonized by large numbers of bacteria (7, 8). Therefore, Gram stain and culture of sputum samples are basically useless in the diagnosis of bacterial pneumonia in these patients. Because of this problem, we asked whether determination of antibody coating of bacteria in bronchial secretions would be of value in the diagnosis of bacterial pneumonia. As a preliminary approach, it first became necessary to determine whether patients with stable chronic bronchitis normally have bacteria in their airway secretions that are antibody coated. We report here that 18 of 25 patients with stable chronic

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TABLE

Antibody Coating of Bacteria in Sputum and Bronchial Wash Samples

	Sputum*					Bronchial wash*				
Stain	No.	0	1+	2+	3+ (%)†	No.	0	1+	2+	3+ (%)†
IgA	21	5	4	7	5 (76)	25	15	7	1	2 (40)
IgG	21	2	9	4	6 (91)	25	11	7	6	1 (56)
IgM	21	8	5	7	1 (62)	25	16	9	0	0 (36)
Ig3	21	4	6	6	5 (81)	25	14	6	3	2 (44)

* 0 = <5 organisms/oil immersion field (OIF), 1+ = 5–10/OIF, 2+ = 10–20/OIF, 3+ = >20/OIF.

† Percent of samples demonstrating 1+ or greater staining.

bronchitis had bacteria in bronchial secretions that were coated with IgG, IgA, or IgM, and all but one had bacteria in sputum samples that were coated with one or more of the antibodies.

Methods

Patient Selection and Characteristics. Twenty-five patients were selected for the study. All had chronic bronchitis as defined by daily sputum production for at least 3 months out of each of the two previous years. All were men between the ages of 47 and 85; all were cigarette smokers. During their hospitalization, all underwent fiberoptic bronchoscopy for evaluation of localized pulmonary densities as identified on chest roentgenograms or because of hemoptysis.

Collection of Specimens. Early-morning sputum samples were collected from the patients on the day of bronchoscopy. Fiberoptic bronchoscopy was performed with an Olympus BF 5B2 instrument (Olympus Corp., New Hyde Park, NY). Premedication included atropine sulfate, 0.6 nmole (0.4 mg); meperidine hydrochloride, 0.2 nmole (50 mg); and pentobarbital sodium, 0.44 nmole (100 mg), administered intramuscularly 30 min prior to the procedure. Topical anesthesia was obtained with 4% lidocaine hydrochloride spray instilled into the nose and oropharynx. The larynx was anesthetized with 2 ml of 2% lidocaine hydrochloride administered through the bronchoscope, which was passed transnasally without the use of a nasotracheal tube. A bronchial wash sample was obtained from the mainstream bronchus of the lung without roentgenographic abnormalities by instillation of 10 ml of nonbacteriostatic saline and suctioning back the fluid into a sterile collection chamber.

Determination of Immunofluorescence. The sputum and bronchial wash samples were mixed with acetylcysteine (1–2 ml) to digest mucus. Then the samples were centrifuged at 1,000 × *g* for 5 min. The supernatant was discarded and the sediment was resuspended and centrifuged a total of three times in 5 ml of phosphate buffered saline (PBS). After the third washing, slides were prepared for Gram stain. Then 0.5-ml aliquots were added to separate tubes containing 1:20 dilutions of fluorescein-labeled antihuman globulins monospecific for IgA, IgG, and IgM (Calbiochem-Behring Corp.) and to a tube containing a similar dilution of a mixture of the three globulins (Ig3, Calbiochem-Behring Corp.). Fluorescein-labeled antihuman albumin was added to an additional tube as a control for nonspecific fluorescence.

After incubation for 30 min at 37°C, the samples were centrifuged, washed with PBS, carefully resuspended, and placed on microscopy slides with coverslips. The slides were evaluated by use of a microscope by three investigators using oil immersion magnification (×1,250). Nine fields were selected at random, and the mean number of bacteria displaying fluorescence was calculated. The number of organisms displaying fluorescence per oil immersion field (OIF) was quantitated as follows: 0 = <5/OIF, 1+ = 5–10/OIF, 2+ = 10–20/OIF, and 3+ = >20/OIF. All slides demonstrating 1+ or greater staining were considered positive if nonspecific staining was absent using the antihuman albumin control.

Results

Twenty-five patients were included in the study. None of the patients had viral or bacterial pneumonia or exacerbations of chronic bronchitis. All underwent fiberoptic bronchoscopy for evaluation of localized pulmonary abnormalities seen on chest roentgenograms or because of hemoptysis. None had changes on chest roentgenograms suggesting postobstructive pneumonia. Eventually 14 patients were found to have bronchogenic cancer, and one to have a hamartoma. In 10 no specific diagnosis was made other than chronic bronchitis.

The results of immunofluorescence staining are shown in the Table. Evaluation of sputum from 21 patients revealed that 76%, 91%, and 62% of the samples demonstrated 1+ or greater staining for IgA, IgG, or IgM, respectively. In bronchial samples positive staining was seen in 40%, 56%, and 36%, respectively. Both coccal and bacillary forms stained positively. Evaluation of Gram stains revealed that five or more bacteria per OIF were present in all sputum samples and in 60% of the bronchial samples.

Comparison of the immunofluorescence-staining patterns in sputum and bronchial secretions revealed that patients with the greatest number of organisms demonstrating fluorescence in sputum had the greatest number in bronchial samples. Samples from only one patient demonstrated a higher number of positively staining organisms in the bronchus as compared to the sputum. In bronchial samples there was no consistent pattern regarding staining with specific antibodies. Seven samples were positive for all three antibodies, one for two (IgA, and IgG), and 10 for a single antibody. Among the latter, 6 stained for IgG, 2 for IgA, and 2 for IgM. None of the samples that stained positively for IgM demonstrated greater than 1+ staining.

Discussion

In this study of 25 patients with chronic bronchitis who did not demonstrate exacerbations of their disease or pneumonia, we found that 20 of 21 sputum samples and 18 of 25 bronchial wash samples contained bacteria that were coated with IgG, IgA, or IgM. Previously, in a study to evaluate the usefulness of determining antibody coating to diagnose bacterial pneumonia, Winterbauer et al found that antibody coating was present in association with 24 of 33 episodes of clinically defined lower-respiratory-tract infections, whereas antibody coating was found in only 1 of 60 control patients (6). Although not stated, presumably none of the control patients had chronic bronchitis.

We elected to study patients with chronic bronchitis because the diagnosis of bacterial pneumonia by use of Gram stain or culture is particularly difficult in this group. This is because the airways are colonized with several types of bacteria known to cause pneumonia (7, 8). Our findings indicate that determination of antibody coating of bacteria has little potential value in diagnosing bacterial pneumonia in this group of patients. The results contrast with studies involving the urinary tract, which have revealed that bacteria do not become antibody coated in association with colonization of the lower urinary tract (9, 10).

The methods used in our study are comparable to those used by Winterbauer et al (6). The samples were aspirated from the side channel of the fiberoptic bronchoscope into a sterile collection container. By the nature of the procedure, it is possible that some of the samples were contaminated by organisms from the oropharynx. Samples were obtained from the "normal" lung in patients with localized pulmonary densities. As defined by Winterbauer et al, smears were considered positive when five or more bacteria per oil immersion field demonstrated fluorescence (6), and organisms did not demonstrate nonspecific staining with the antihuman albumin control.

Comparison of the patterns of staining with the monospecific antiglobulins revealed that some samples stained with only one of the agents, whereas others stained with two or three. Since there was no particular pattern when staining occurred with only one of the agents, some bacteria staining with IgA, IgG, or IgM, the results suggest that the possibility of a characteristic staining pattern being found in association with bacterial pneumonia is unlikely. However, we did not specifically evaluate patients with chronic bronchitis who also had bacterial pneumonia. Therefore, we do not know whether the absolute number of positively staining organisms increases significantly with the development of bacterial pneumonia.

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Spinal Anesthesia for the High-Risk Infant

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Abstract

Spinal anesthesia is gaining in popularity as an alternative to general anesthesia in high-risk infants. We present five cases of high-risk infants, each with a history of apnea, compromised airway, full stomach, major system disease, or some combination of those conditions, who underwent lower-abdominal surgical procedures under spinal anesthesia. Indications for, technique of administration of, and management of spinal anesthesia in this group of patients are discussed.

Enthusiastic reports of spinal anesthesia for children date back to the early 1900s (1, 2). The advent of this form of anesthesia for children resulted in marked reductions in intraoperative mortality and morbidity (3, 4). At a time when the agent of choice for pediatric anesthesia was chloroform, the introduction of spinal anesthesia was welcomed for its many advantages, including safety, muscle relaxation, and absence of postoperative vomiting and pain. With the introduction of muscle relaxants, halothane, and improved monitoring techniques, the use of regional anesthesia in pediatric patients was virtually abandoned (5), and a generation of anesthesiologists rarely observed or performed a regional block in a child. In 1984, Abajian et al (6) reintroduced the concept of regional anesthesia as a viable alternative to general anesthesia in a high-risk pediatric population, including preterm infants and survivors of neonatal intensive-care units. We present five cases of high-risk infants who underwent spinal anesthesia for abdominoinguinal surgical procedures.

Case Reports

Case 1. A 4-month-old, 6-kg male infant presented for bilateral inguinal hernia repair. The patient had undergone successful repair of a tracheoesophageal fistula (TEF) shortly after birth. The postoperative course had been marked by significant upper-airway obstruction requiring aggressive respiratory therapy in the neonatal intensive-care unit. Significant stridor and hypoventilation had eventually resolved. Following discharge, the infant had thrived except for stridor, considered to be secondary to laryngotracheomalacia.

After informed consent had been obtained from the parents, spinal anesthesia was planned. The infant was not premedicated, and intravenous administration of dextrose 5% in 0.2% saline solution began when the infant arrived in the operating room. Monitoring was established with standard EKG, automated blood pressure monitor, and pulse oximeter. With the patient in the sitting position, a 22-gauge, 1.5-in. spinal needle (Becton Dickinson and Co., Rutherford, NJ) was inserted via the L3–4 interspace, and clear cerebrospinal fluid (CSF) was obtained. Tetracaine, 1% in a dose of 0.4 mg/kg, made hyperbaric with a similar volume (0.24 ml) of 10% dextrose, was injected into the subarachnoid space.

Surgery proceeded uneventfully and was completed in 65 min. A motor and sensory block to approximately a T6 level as estimated by pinprick was obtained and lasted for a total of 95 min. The infant appeared comfortable during and after the operation, requiring only small doses of intravenous ketamine (0.25 mg/kg) to control movements of the upper extremities. The infant

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tolerated feedings immediately following admission to the recovery room. The infant was discharged from the recovery room 2 hr after completion of surgery. No postanesthesia complications were noted.

Case 2. A 43-week-conceptual-age, preterm female infant was to undergo elective bilateral inguinal hernia repair. The infant was born at 32 weeks' gestation weighing 2.1 kg. She required ventilatory assistance for respiratory distress syndrome, apnea, and patent ductus arteriosus, all of which resolved. Her weight prior to surgery was 4.2 kg; hematocrit was 0.26. The infant had had nothing by mouth for 4 hr and received no premedication.

A lumbar puncture was performed at the L3–4 interspace with the child being held in a sitting position with the head extended, while being monitored as in case 1. A dose of 1.8 mg of 1% tetracaine, made hyperbaric with a similar volume of dextrose 10% in water, was injected through a 22-gauge, 1.5-in. spinal needle. Sensory level, by reaction to needle prick, was estimated to be at T6. After 2 min, a solid motor block was established in the lower extremities, where an intravenous infusion was started without resistance by the infant. No changes in blood pressure, heart rate, temperature, or oxygenation were noted. A small dose of intravenous ketamine (0.25 mg/kg) was given for sedation.

The child slept throughout the surgical procedure, which was uneventful. Seventy-five minutes following the spinal block the infant was transported to the recovery room, where she was fed. A full range of lower-extremity movements was noted 15 min later. The infant was then discharged to the pediatric ward for observation. There were no complications due to anesthesia or surgery.

Case 3. A 9-day-old male infant with the diagnosis of prune-belly (Eagle-Barrett) syndrome, polycystic kidneys, acute renal failure, and small ventricular septal defect was brought to the operating room for insertion of a peritoneal dialysis catheter. The patient weighed 3.8 kg. Relevant laboratory studies were potassium of 6.2 mmol/liter and creatinine of 486 μmol/liter (normal range 50–110). A spinal block was performed using 2.2 mg of hyperbaric tetracaine to achieve a sensory level of T4. The incision was supraumbilical. Surgery and anesthesia proceeded without complications, and the child received maintenance intravenous fluids. No significant changes in blood pressure, heart rate, or oxygenation were noted. Following the procedure, the patient was awake, had adequate movement of the lower extremities, and was transferred to the neonatal intensive-care unit.

Case 4. A 44-week-conceptual-age, 5.4-kg male infant had bilateral inguinal hernias needing repair. He was born at 31 weeks' gestation and his neonatal course was complicated by apnea. The infant had remained on an apnea monitor at home. A spinal anesthetic was administered as described earlier using 0.4 mg/kg of 1% hyperbaric tetracaine in the L3–4 interspace. Surgery proceeded uneventfully and no intraoperative or postoperative complications were noted. The infant was discharged from the recovery room to the pediatric ward and kept overnight on an apnea monitor.

Case 5. A term 14-day-old male infant weighing 3 kg had an incarcerated right inguinal hernia and vomiting. A spinal block was performed using a similar technique to achieve a T6 level of block. Hyperbaric tetracaine in a total dose of 1.4 mg was used. Anesthesia and surgery were accomplished uneventfully and the infant slept throughout the procedure. The postoperative course was also uncomplicated.

Discussion

The use of regional anesthesia in infants undergoing surgery is enjoying a renaissance. In describing a series of 300 spinal anesthetics in infants and children in 1910, H. Tyrrel-Gray stated: "The advantages to be gained by the use of spinal anesthesia have so far impressed me that I am convinced it will occupy an important place in the surgery of children in the future" (4). However, spinal anesthesia fell into relative disuse until recently, mainly because of the safety record of general anesthesia, the need for heavy premedication in older children, and the need for anesthesiologists familiar with and skilled in the technique.

Preterm infants are clearly predisposed to apnea, hypoxia, and cardiovascular instability (7–18). General anesthesia, involving the use of inhaled anesthetics, narcotics, and muscle relaxants, increases the incidence of postoperative apnea (9, 10, 14–18). The incidence of apnea in surviving preterm infants requiring anesthesia has been reported to be as high as 25% (14). Liu et al found that 6 of 41 preterm infants recovering from surgery required reintubation secondary to apnea (9). Steward reported postoperative apnea in 6 of 33 preterm infants requiring general anesthesia (10). In a recent editorial, Gregory and Steward advised avoiding elective surgery in children of less than 44 weeks' postconceptional age (gestational age + extrauterine life) because of the high incidence of apnea (15). Unfortunately, however, pediatric surgeons have repeatedly noted a high incidence of incarceration and life-threatening intestinal obstruction in the youngest infants with untreated inguinal hernias and emphasize the danger of delaying surgical repair in this age group. In a recent report of 100 consecutive infants less than 2 months of age having inguinal hernia repairs, 31 had incarcerated hernias (19). The authors support the current pediatric surgical practice of operating on premature infants with hernias prior to their first discharge from the hospital.

A regional block (spinal, epidural, caudal) appears to be a practical alternative to general anesthesia in this group of patients. Among the infants considered to be at high risk for postoperative apnea are all preterm infants of less than 44 weeks' postconceptional age, any child with debilitating systemic disease, patients with a compromised airway, and siblings or relatives of infants who have died of sudden infant death syndrome (15, 18).

Another indication for regional anesthesia is the infant or child with compromised respiratory function. Airway or pulmonary complications of mechanical ventilation in preterm infants and newborns are multiple and common (16–18). Frequently, infants who have required mechanical ventilation will develop bronchopulmonary dysplasia. The airway is compromised, even after short-term intubation, owing to squamous cell metaplasia and poor tracheal ciliary activity. General anesthesia in such infants can be complicated by difficult intubation, compromised intraoperative oxygenation, postoperative atelectasis, and stridor (9), all of which could be avoided with regional anesthetic techniques. These considerations led us to decide on a spinal anesthesia for case 1, a term infant with a compromised airway secondary to a recent TEF repair.

The infant with a "full stomach" is a major challenge to the anesthesiologist. The morbidity and mortality associated with passive aspiration of gastric contents in the child have been well documented (20–22). The intravenous rapid-sequence induction technique requires functioning intravenous access and a skilled anesthesiologist in order to avoid aspiration, hypoxia, and hypotension. A regional anesthetic technique is a viable alternative in such cases, in which the risk of aspiration is increased. The protective effect of normal airway reflexes, which are preserved under regional anesthesia, is important in preventing aspiration of gastric contents. The indications for and advantages of spinal anesthesia in high-risk and in normal pediatric patients are summarized in Tables 1 and 2, respectively.

TABLE 1
Indications for Spinal Anesthesia in High-Risk Infants

When general anesthesia poses increased risk
Difficult airway (Treacher Collins, Down's syndrome, laryngomalacia)
Conceptual age less than 44 weeks
Surviving preterm infant with history of
  apnea
  bronchopulmonary dysplasia
  subglottic stenosis
Full stomach (incarcerated hernia, vomiting)

Type of surgery suited to spinal anesthesia
abdominal, inguinal
perineal
lower extremity

Subarachnoid Injection: Techniques and Risks

Performance of a subarachnoid injection in a child is not difficult. It is frequently performed by pediatricians for diagnostic purposes. An average of over 200 spinal taps per house staff member was recorded in one training program in pediatrics (23). These procedures are usually performed by the most junior members of the staff; the incidence of complications is extremely low. The personal experience of one of the authors (NS) reveals no known long-term complications in over 800 spinal taps in pediatric patients, most of whom were preterm infants. The incidence of a "bloody tap" is in the range of 5% (23).

A 22-gauge, 1.5-in. spinal needle with stylet has proven satisfactory for most of these procedures. When a spinal anesthetic is attempted in an infant, it is advisable to carry out the lumbar puncture below the level of the third lumbar vertebra, since the spinal cord terminates at L3 in infants (L2 in adults). Clear CSF must be ob-

TABLE 2
Advantages of Spinal Anesthesia in Non-High-Risk Infants

1. Postoperative pain relief
2. Earlier discharge
3. Decreased narcotic requirement
4. Decreased need for nonnarcotic analgesics
5. Rapid return to alert state
6. Simple and effective technique
7. Safety record
8. Rapid onset
9. Minimal interference with laryngeal reflexes, cough ability, respiration
10. Decreased incidence of postoperative apnea (?)

TABLE 3
Contraindications to Spinal Anesthesia

1. Abnormal hemostasis
2. Hypovolemia
3. Neurologic disease
4. Local infection
5. Allergy to local anesthesia
6. Spina bifida or other spinal defects
7. Lack of parental consent

tained before a subarachnoid injection is attempted. The dose of hyperbaric tetracaine used is between 0.3 and 0.5 mg/kg, the higher dose being required in the younger infants. To this calculated dosage of 1% tetracaine are added an equal volume of dextrose 10% to achieve hyperbaricity and a volume equal to the dead space of the spinal needle (about 0.04 ml in the case of a 22-gauge, 1.5-in. needle). A 1-ml syringe is required to administer the total small volume of drug. After removal of the spinal needle the infant is kept in the supine position. Motor blockade of the lower extremities usually occurs in the first 3 min following subarachnoid injection.

Establishing the upper level of sensory anesthesia is difficult but it is predictably below T4 with use of the dosages just specified, provided that the drug is injected slowly, even if the patient is crying or straining (6, 7, 13, 14, 18). In the personal experience of one of the authors (NS) in over 50 cases, use of the dosages described has never resulted in a "total spinal" block.

In younger infants, less than 3–4 months of age, no prior general anesthesia is needed to perform the spinal block. The infant is held in the sitting or the lateral position with the head extended, care being taken to avoid compromising ventilation. The use of a digital pulse oximeter is helpful during the procedure to diagnose potential desaturation due to an obstructed airway or to restrictive hypoventilation.

TABLE 4
Disadvantages of Spinal Anesthesia in High-Risk Infants

1. Bad reputation; parental anxiety
2. Time-consuming (?)
3. Limited duration
4. Other form of anesthesia may be required
5. Complications:
   hypotension
   postdural headache (?)
   toxicity of local anesthetics
   hypersensitivity to local anesthetics
   neurologic sequelae (?)
6. Prolonged postoperative observation:
   apnea
   airway obstruction
   pulmonary complications

In older children, some form of anesthesia may be required prior to administration of the spinal anesthesia. In such cases we prefer to use a small dose of ketamine (0.25 mg/kg intravenously) or a potent inhaled anesthetic at low concentration with spontaneous ventilation, prior to performing the lumbar puncture. Appropriate airway management is mandatory, and emergency drugs and equipment for resuscitation should be readily available throughout the procedure. The incidence of postoperative apnea using spinal anesthesia has not been reported, but the clinical impression is that it is negligible when appropriate dosages are used. Nevertheless, the infants should be observed in the recovery room and for at least 12 hr postoperatively with an apnea monitor to diagnose and treat apnea if present.

The incidence of clinically significant hypotension following spinal anesthesia in children of less than 5 years is extremely low (23). It has been postulated that this lack of effect is secondary to immaturity of the sympathetic nervous system as well as to the proportionately reduced blood volume in the lower extremities of children, as compared with adults. It therefore seems reasonable to perform the lumbar puncture prior to obtaining intravenous access, and to wait for the sensory block to be established before inserting an intravenous cannula in one of the now anesthetized lower extremities.

The contraindications and disadvantages of regional anesthesia in high-risk infants are similar to those in adults (Tables 3, 4). Parental concerns are usually satisfied by adequate patient selection and reassurance that the child will not have pain and that supplemental anesthesia and/or analgesia will be provided as necessary. It is also important to explain that the anesthetic technique is not experimental and is preferred in certain conditions in which general anesthesia may be associated with a higher incidence of complications.

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Severe Hemolytic Anemia due to Glucose-6-Phosphate Dehydrogenase Deficiency and Epstein-Barr Virus Infection

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Abstract

A 23-year-old man with Epstein-Barr virus infection developed severe hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency.

We recently encountered a patient with glucose-6-phosphate dehydrogenase deficiency who developed severe hemolytic anemia during the course of an Epstein-Barr virus mononucleosis infection. We previously encountered a similar patient who developed a severe hemolytic episode as a result of a cytomegalovirus infection (1).

Case Report. A 23-year-old white man of eastern European descent, with a known glucose-6-phosphate dehydrogenase deficiency, was hospitalized with a 5-day history of spiking temperatures to 103.4°F. Three days prior to admission he noted a mild sore throat, severe malaise, anorexia, and diaphoresis. No medications were taken except acetaminophen. Laboratory studies prior to hospitalization revealed a hematocrit of 29 vol %, LDH 469 IU/L, bilirubin 1.8 mg/dl. The prior hematocrit had been 45 vol %.

The history revealed that the patient had been diagnosed as having a glucose-6-phosphate dehydrogenase deficiency when he was 6 years old and was evaluated for moderate anemia. There were five prior hospitalizations for severe hemolysis associated with presumed viral infections. The patient's father had factor XI deficiency. The patient's usual hemoglobin and hematocrit were normal.

On examination he appeared acutely ill and pale. The blood pressure was 120/70 mm Hg, pulse 103, and temperature 102.4°F. The pharynx was erythematous, and there were vesicles and petechiae on the soft palate. Anterior shotty cervical nodes were found. Chest and heart examinations were normal. The liver was not enlarged. The spleen was palpated 1 cm below the left costal margin.

Laboratory findings included: hemoglobin 9.8 gm/dl, hematocrit 29.1 vol %, white blood count 6,600/mm^3, with 48% polys, 9% bands, 35% lymphocytes (most atypical), 7% monocytes, 1% metamyelocytes. Platelets were 213,000/mm^3. The peripheral smear revealed polychromasia, and reticulocytes were 3.5%. A direct antiglobulin test was negative. The alkaline phosphatase was 349 IU/L. The aspartate aminotransferase was 70 IU/L, alanine aminotransferase 53 IU/L, bilirubin 2.3 mg/dl, indirect bilirubin 2.0 mg/dl, LDH 1,066 IU/L, and haptoglobin <1 mg/dl. A throat culture grew normal flora and a monospot test (Ortho Kit) was positive. An EBV-IFA was <64, and EBV-IgM was 40 (normal 0–9).

On the second hospital day, severe weakness and orthostatic hypotension developed. The hemoglobin was 7.3 gm/dl. After transfusion with three units of washed packed red blood cells, the

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hemoglobin stabilized at 10.4 gm/dl. Within two weeks the hemoglobin had risen to 15.0 gm/dl. The spleen became nonpalpable two months later, and the liver chemistries normalized.

Discussion. Like the patient previously reported, this patient developed a severe hemolytic episode during the course of a mononucleosis syndrome. Most hemolytic episodes associated with Epstein-Barr virus infections are due to cold agglutinins with an anti-i specificity, but severe hemolysis is unusual (2). In this patient, spontaneous recovery occurred with resolution of the infection, as noted in the patient reported with hemolysis associated with cytomegalovirus infection (1). Hemolytic episodes in patients with glucose-6-phosphate dehydrogenase deficiency are usually caused by certain drugs or infections. This is the first report of its association with an Epstein-Barr virus infection.

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Charcot Shoulder as the Initial Symptom in Arnold-Chiari Malformation with Hydromyelia: Case Report

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The case of a 59-year-old woman with a Charcot shoulder associated with hydromyelia and an Arnold-Chiari malformation is discussed. Charcot joints are an exceptionally rare presentation of Arnold-Chiari malformations. Appropriate surgical repair of the malformation is essential once the radiologic diagnosis has been made.

Although Charcot joints are common in patients believed to have spinal cord cavitation, their association as the initial symptom with Arnold-Chiari malformations is decidedly rare (1–4). Profound neurologic deficits usually first bring the patient to medical evaluation, the development of Charcot joints being a late complication of hydromyelia. Recently, a woman with a Charcot shoulder was evaluated at our institution and found to have hydromyelia associated with an Arnold-Chiari malformation.

Case Report. A 59-year-old woman reporting four months of painless right shoulder swelling and limitation of movement was evaluated by an orthopedic surgeon. Further history revealed that the patient had noticed increasing difficulty with ambulation and coordination for approximately one year. She had experienced numbness of the upper and lower extremities for the past nine months.

Examination. The right shoulder was noted to be enlarged and crepitant, with no tenderness or fluctuance on palpation. Passive range of motion was preserved, although the patient was only able to abduct the arm 15% of normal. Deficits on neurologic examination were as follows: All divisions of the left trigeminal nerve revealed decreased sensation to pinprick, light touch, and vibration. There was marked horizontal nystagmus on left lateral gaze. The uvula deviated to the right. Deficits in motor strength included left interossei 3/5, right supraspinatous 3/5, right deltoid 2/5, right infraspinatous 0/5, and right teres major 0/5. Sensation in all modalities was decreased on the left with a relative sensory level at T10. Sensation over the right shoulder was virtually absent. The patient was hyperreflexic throughout with bilateral Babinski's. There was mild left-sided dysmetria.

Radiologic examination. X-ray examination of the right shoulder revealed complete destruction of the joint with marked soft tissue swelling, consistent with Charcot arthropathy (Fig. 1). Magnetic resonance imaging of the brain and spinal cord revealed an Arnold-Chiari malformation with hydromyelia. Part of the cerebellum was noted to be displaced through the foramen magnum to the lower border of C1. The hydromyelic cavity was seen to extend from the thoracic cord tapering superiorly to the level of the fourth ventricle (Fig. 2).

Operation. Using the principle of microsurgical reconstruction of the cisterna magna developed by Malis (6) in 1972, operative correction was carried out. The patient was positioned semisitting. A bilateral suboccipital craniectomy and C1 laminectomy was performed. Upon opening the dura, the cerebellar tonsils were noted to extend through the foramen magnum to the level of C1. A clear indentation in the tonsils was observed. This deformity was felt to arise from the bony compression and a thickened dural band at

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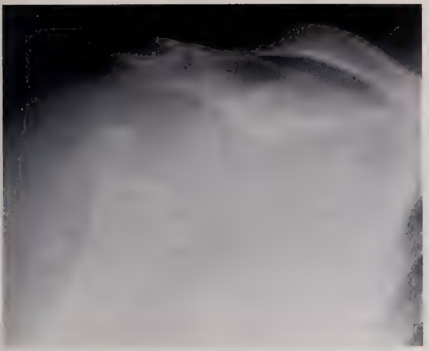

Fig. 1. Plain x-ray of right shoulder revealing Charcot joint. There is marked soft-tissue swelling with destruction of joint capsule and head of humerus.

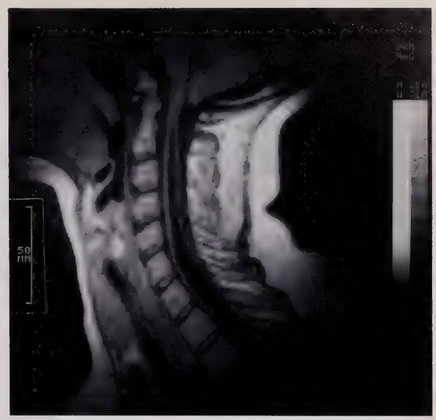

Fig. 2. MRI revealing hydromyelia associated with Arnold-Chiari malformation. Cerebellar tonsils are visible below level of foramen magnum. Central cavitation of the spinal cord is visible from spinomedullary junction to midthoracic region.

the level of C1. The cisterna magna was devoid of cerebrospinal fluid. Using the operating microscope, a midline 2-cm incision was made in the arachnoid over the vallecula. Adhesions between the tonsils were then lysed. Further dissection revealed the foramen of Megendie to be imperforate. Membranous adhesions were sharply dissected allowing entrance into the fourth ventricle. At this point cerebrospinal fluid was observed to flow freely out of the fourth ventricle superiorly and from the dilated central cord cavity inferiorly. Once the cerebrospinal fluid pathways were reestablished, the previously divided arachnoid was closed watertight with a continuous suture of 10/0 nylon. No attempt was made to close the dura, as it was felt that the dural band was part of the pathologic compression of the tonsils. The exposed dura was covered with gelfoam. The remainder of the wound was closed routinely in multiple layers.

Discussion. Charcot or neuropathic joint has been associated with tabes dorsalis, diabetes, and hydromyelia (1, 3, 5). Thirty years ago, 90% of neuropathic arthropathies were related to tabes dorsalis, the remainder of cases being distributed among the other disease entities. With the control of syphilis, hydromyelia may now account for a substantially larger proportion of those patients having Charcot joints.

The process involved in the formation of Charcot joints is thought to result from repeated trauma sustained by a joint that has lost its protective sensory perception (1, 3). With the absence of pain sensation, repeated misuse of the joint produces cumulative damage (3). Patients may then develop a painless, swollen, deformed joint. Approximately 80% of Charcot joints found in association with hydromyelia involve the upper extremity (3). Affected joints are painless in one half of these patients (2).

Arthropathies, Charcot joints, or both develop in 25% of patients with hydromyelia (3). In the presence of an Arnold-Chiari malformation, hydromyelia is found in 52% of the patients undergoing operative repair (2). Given the associations of the Arnold-Chiari malformation with hydromyelia and of hydromyelia with Charcot joints, notably few reports of Arnold-Chiari malformation with Charcot joints have been published.

Part of the discrepancy may be resolved in terms of nomenclature. Although used interchangeably in the literature, the terms hydromyelia and syringomyelia refer to distinct pathologic entities. Hydromyelia appropriately refers to a dilated central canal secondary to an obstruction of the foramen of Magendie, usually part of an Arnold-Chiari malformation, and is exclusive of a syrinx caused by tumor or trauma. Arnold-Chiari malformations involve varying anomalies of the cervicomedullary junction, and most often occur with significant bulbar or cord dysfunction (2, 4). In this group, neuropathic joints represent a late sequelae of disease, with treatment often sought upon early neurologic dysfunction. The patient reported on here had a history of significant though not incapacitating disesthesias of the upper and lower extremities.

Of the 127 cases of Arnold-Chiari malformation reviewed by Levy et al in 1983, no patient had a neuropathic arthropathy (2). Only one patient had evidence of a Charcot joint, which involved the cervical spine (2). Paul et al reviewed 71 cases of the Arnold-Chiari malformation and found no Charcot joints (4). Malis' personal series of over 40 Arnold-Chiari malformations does not contain a single case of a Charcot joint (6; personal communication, March 1987). Surprisingly, 2 cases almost identical to our own patient were reported by Sackellares and Swift in 1976 (5). These patients had painful shoulder enlargement and were subsequently found to have hydromyelia and Arnold-Chiari malformations.

Although rare, Charcot joint may be a sign of an occult Arnold-Chiari malformation. Demonstration of a syrinx alone should not be considered definitive proof of the underlying pathology. Appropriate radiologic investigation with MRI of the spinal cord and spinomedullary junction should be undertaken to eliminate the possibility of an associated Arnold-Chiari malformation.

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Hemophilia A and Ulcerative Colitis: Case Report

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Hemophilia A is an X-linked, recessively inherited bleeding disorder which results in defective synthesis of Factor VIII (FVIII) protein; it has been associated with different disorders. We report a case in which ulcerative colitis occurred in a patient affected by severe hemophilia A, an association described by Radensky et al (1). Once triggered by ulcerative colitis, the hemostatic deficiency greatly heightens gastrointestinal bleeding symptoms, calling for specific control measures. The prognosis of such cases must, therefore, take into account the high risk of bleeding of these patients, as well as the need for specific measures to treat the hemorrhagic symptoms.

Case Report. A 21-year-old man with severe hemophilia A was admitted to the hospital because of an 8-week history of intermittent bloody diarrhea, tenesmus, malaise, anorexia, weight loss of 18 lb, continuous fever of about 38°C, and intermittent abdominal burning pain. The patient was not on drugs, nor had he been infused with Factor VIII concentrates for over 2 months, when he last required this therapy because of hemarthrosis of the right elbow. Two days prior to admission, the patient developed persistent, intensive abdominal burning pain. His stool became bloody, his temperature rose to 39°C, and his right knee was painful, warm, and swollen. The patient's baseline level of Factor VIII was 0.01 IU/ml, and no inhibitory activity had ever been demonstrated in his plasma. There was no family history of inflammatory bowel disease.

Examination revealed temperature 39.1°C, blood pressure 140/70 mm Hg, pulse rate 100/min regular. There was no lymphadenopathy, and the skin was normal. Abdominal examination revealed diffuse abdominal tenderness; bowel sounds were normal. Acute inflammatory signs, including heat, pain, and swelling, were observed on the right knee, as well as partial impairment of joint movements. Other physical findings were normal.

Laboratory studies showed the following values: Hb 10.2 gm/dl, HCT 32%, RBC count 3.6 $\times 10^{12}$/L, WBC count 7.6 $\times 10^{9}$/L with 3,525 lymphocytes/ml and no left shift, platelets 276,000/ml, and erythrocyte sedimentation rate 60 mm/first hour. Prothrombin time was 12.5 sec (control 12.0 sec), and Factor VIII:C was 0.01 IU/ml as tested by the APTT method using FVIII-deficient plasma as a substrate. There was no inhibitory activity against FVIII:C by Bethesda assay. Hepatic, renal, protein, and lipids serum levels were normal. Anti-HIV was positive by ELISA assay. Stools were also positive for occult blood, whereas stool cultures for ova, parasites, *Salmonella,* and *Campylobacter* were negative, as were blood, urine, and joint serous fluid cultures. Serologies were irrelevant.

Simple roentgenograms of the thorax and abdomen were normal. Barium enema showed mucosal irregularity in the ascending and sigmoid colon and rectum. Fibrocolonoscopy revealed multiple circumscribed erythematous lesions with diffusely friable and granular mucosa affecting the ascending and sigmoid colon and rectum, largely suggesting an ulcerative colitis pattern. Biopsy specimens revealed marked crypt loss; remaining crypt showed prominent distor-

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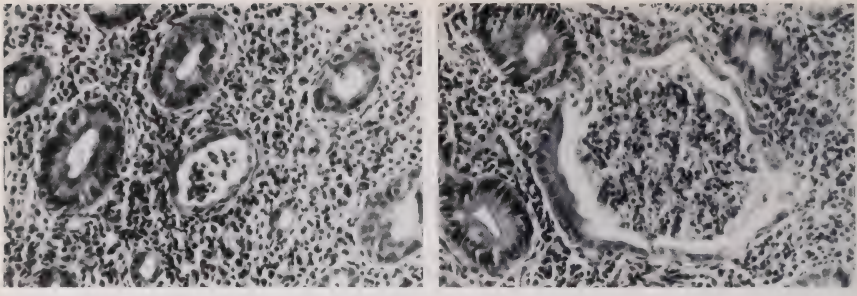

Fig. Microphotographs of sigmoid colon section demonstrating gross infiltration with inflammatory cells, crypt abscesses, and reduction in number of glands.

tion and mucin depletion of the epithelial cells. The muscularis mucosae contained scattered chronic inflammatory cells. The mucosa showed a markedly generalized atrophy; and small foci of hemorrhages, as well as epithelioid histiocytes with multinucleated giant cells, were observed in the tunica propria mucosae (Fig.).

After the first day of hospitalization, severe rectal hemorrhages developed, and the patient's Hb fell to 7.9 gm/dl. A total of 4 IU of packed RBC and 6,000 IU of Factor VIII were transfused throughout the next 72 hr, which allowed bleeding to stop. Immediately after the ulcerative colitis diagnosis was established, 80 mg/day methylprednisolone and 2 gm/day salazopyrine were started. Gastrointestinal bleeding was not observed until discharge. Remaining symptoms gradually disappeared, and the patient was discharged after 22 days of hospitalization. Nineteen months later, 2 gm/day salazopyrine is being maintained, and the patient remains asymptomatic. The follow-up colonoscopic examinations have continued to be normal.

Discussion. A case of ulcerative colitis has previously been described as associated with severe hemophilia A (1). Although bleeding in the gastrointestinal system is not one of the most frequent symptoms observed in hemophiliacs (2), it is usually a severe complication when it does develop and must therefore be vigorously managed. Replacement therapy, for both the Factor VIII deficiency and the blood loss, is absolutely essential, and these measures need to be accompanied by treatment of any underlying disease.

Patients affected by ulcerative colitis have otherwise been reported to have a "hypercoagulable" state, which puts them at high risk for the development of thromboembolic phenomena. In practice, massive gastrointestinal bleeding is not frequently seen in ulcerative colitis (3). In our patient, severe digestive hemorrhage developed, and 6,000 IU of Factor VIII concentrate had to be transfused for 3 days to stop the bleeding.

Bowel alterations due to ulcerative colitis can initiate bleeding, but, according to Radensky et al (1), severe hemorrhages are largely attributable to the concommitant hemostatic disorder.

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Endometrial Carcinoma with Uterus Didelphys

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Endometrial carcinoma is the most common malignancy of the female genital tract. Diagnosis of this malignancy may be more difficult when the disease is present in uterus didelphys. We present a case study of a patient with this malignancy in uterus didelphys.

Case Report. The patient was a 60-year-old para 1, gravida 0. Her last menstrual period was at age 56, with no postmenopausal bleeding. The patient had no prior surgery and took no medications. On initial gynecologic examination, a complete vaginal septum and two cervices were identified. Papanicolaou smears were IA, and on all follow-up visits after 1978, both cervices were normal. In November 1984, the patient reported vaginal spotting. An aspiration curettage showed adenomatous hyperplasia without atypia in the left horn. Three cycles of Provera at 20 mg/day were taken by the patient. Uterine bleeding persisted after this regimen. In March 1985, a bilateral dilatation and curettage was performed. Curettage of the right cavity demonstrated inactive endometrium, and severe adenomatous hyperplasia was identified in the left cavity (Fig. 1). Endocervical curettage was normal. Hysterectomy was advised.

Preoperative chest radiogram, intravenous pyelogram, mammogram, and colonoscopy were all unremarkable. Sonography revealed normal postmenopausal anatomy, but failed to identify the left ovary. Serum follicle-stimulating hormone and estradiol levels were in the postmenopausal range.

The patient was admitted to The Mount Sinai Hospital in November 1985, where she underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy. There were no intraoperative or postoperative complications, enlarged lymph nodes, or evidence of intraabdominal implants. Sagittal section of the specimen demonstrated the two separate uterine cavities (Fig. 2). The left cavity contained a tan papillated mass. Histologic section demonstrated well-differentiated adenocarcinoma infiltrating through two-thirds of the myometrium (Fig. 3). Also present were areas of benign squamous metaplasia (Fig. 4). In the right cavity, the endometrium was inactive. There was no evidence of lymphatic or venous invasion. The right ovary, both fallopian tubes, and parametria were unremarkable, and both cervices showed chronic inflammation. The left ovary was absent.

Radiotherapy to the pelvis and paraaortic lymph nodes was performed because of the specific depth of invasion. The patient tolerated a total of 5,000 rads over a five-week course, with no evidence of recurrent disease to date.

Discussion. Prognosis depends on several factors, including stage, nodal involvement, histologic grade of tumor, depth of penetration, and cell type (1). In general, clinical stage I adenocarcinoma of the uterus has an overall reported five-year survival rate of approximately 74% (1, 2).

A recent corroborative study noted an overall 10% incidence of lymph node metastasis in stage I disease; of these, 2.2% were grade I, 11.4% were grade II, and 26.8% were grade III (2). Additionally, in clinical stage I disease, a 20%–25% risk of pelvic node metastasis was noted when the outer third of the myometrium was involved with grade I tumor (2).

The tumor grade is the one factor obtainable preoperatively which correlates with myometrial

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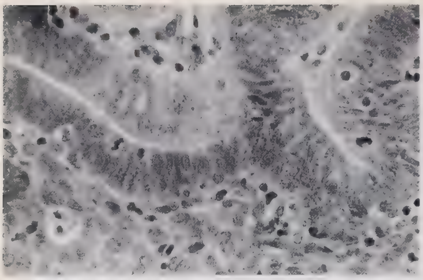

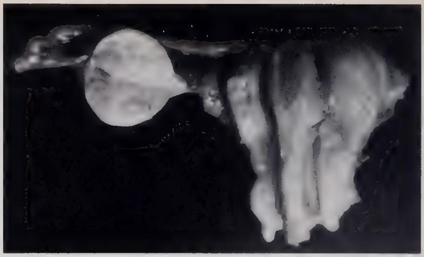

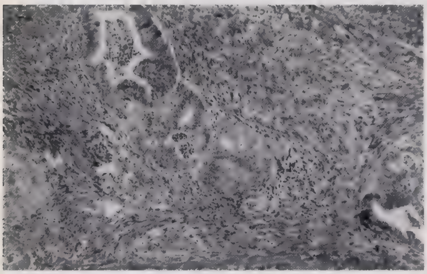

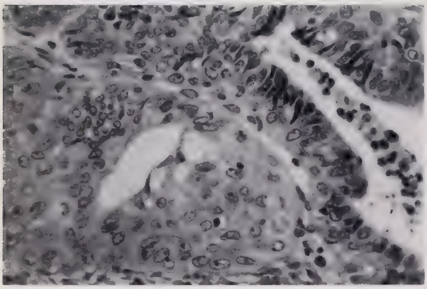

Fig. 1. Upper left Curettage of left uterine cavity showing severe adenomatous hyperplasia of endometrium. Note crowded glands, piling up of epithelial cells, and mitotic activity (H&E, original magnification ×40).

Fig. 2. Upper right Gross specimen demonstrating two separate endometrial cavities and two cervices.

Fig. 3. Left Well-differentiated adenocarcinoma infiltrating through myometrium. Note also acute inflammatory exudate in neoplastic glands (H&E, original magnification ×25).

Fig. 4. Below Benign squamous metaplasia adjacent to well-differentiated adenocarcinoma (H&E, original magnification ×40).

penetration (1). Overall five-year survival rates are 80% with grade I, 66%–74% with grade II, and 50% with grade III tumors (3, 4). Tumor depth of myometrial penetration also appears to correlate with lymph-node involvement; superficially invasive tumors have an 85% cure rate, whereas deeply invasive lesions have a 60% five-year cure rate (3, 4).

Although this patient had a favorable grade of tumor, the depth of involvement significantly increased the likelihood of occult nodal spread, thus necessitating radiotherapy.

Mullerian anomalies have not been implicated as a significant risk factor for development of cervical, uterine, or ovarian malignancies; however, several reports describe the existence of various tumors in anomalous uteri (5–14). One report describes the simultaneous occurrence of atypical hyperplasia and adenocarcinoma in separate horns of uterus didelphys (5). Another report describes synchronous involvement of both cervices with squamous cell carcinoma in another patient with uterus didelphys (10).

The treatment of endometrial carcinoma in uterus didelphys is the same as with a single uterus, but the management of this tumor is made more problematic by the presence of two horns. The relationship of prognosis to tumor grade, degree of myometrial penetration, stage, and nodal involvement cannot be overemphasized. However, each horn may be affected independently; carcinoma may affect one horn only or both horns simultaneously, or different lesions may be present in each horn.

The presence of endometrial cancer in the left horn and inactive endometrium in the right horn demonstrates that hormonal factors are not necessarily the most important ones in the etiology of this patient's endometrial cancer. Indeed, overall survival rates in the anomalous uterus appear to depend only on stage, nodal involvement, histologic grade, depth of penetration, and cell type, rather than on the anomaly itself, except in the rare instance in which the duplication is unrecognized and incomplete sampling is done.

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Bronchoalveolar Lavage in a Patient With Malignant Histiocytosis and the Adult Respiratory Distress Syndrome

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Abstract

Bronchoalveolar lavage (BAL) was performed on a 36-year-old woman with fever, abdominal pain, diffuse alveolar infiltrates, and respiratory failure. Highly atypical histiocytic-monocytoid cells with erythrophagocytosis, typical of malignant histiocytosis, were obtained, along with red blood cells and polymorphonuclear leukocytes. The diagnosis of malignant histiocytosis was established by bone marrow examination on the same day. After two weeks of chemotherapy, there was significant radiographic and clinical improvement. Repeat BAL at that time showed an absence of atypical cells, red blood cells and polymorphonuclear leukocytes. This is the first report of the use of bronchoalveolar lavage to confirm pulmonary involvement in malignant histiocytosis.

Malignant histiocytosis (MH), or "histiocytic medullary reticulosis" (1), is a rare hematologic disorder which is characterized by a neoplastic proliferation of atypical histiocytes. It represents a malignant disorder of the monocyte-macrophage lineage together with acute monoblastic leukemia (AMoL). There is support for a relationship between AMoL and MH with transitional forms between the two entities. The clinical picture is dominated by fever, wasting, hepatosplenomegaly, lymphadenopathy, and cytopenia (2); leukocytosis may be present in some patients (3). Pulmonary involvement as demonstrated by roentgenograms, open lung biopsy, or autopsy has been reported (4, 5); however, only a few cases of respiratory failure as the dominant presentation have been described (6, 7). No cases presenting with recognized adult respiratory distress syndrome (ARDS) have been published. We report a 36-year-old woman with ARDS in whom pulmonary involvement with malignant histiocytosis complicated by intraalveolar hemorrhage was demonstrated by bronchoalveolar lavage (BAL).

Case Report. A 36-year-old white woman came to the emergency room with a 2-week history of fever, chills, headaches, lower abdominal discomfort, and vaginal discharge. There was no previous history of any illness or intravenous drug abuse.

Her temperature was 99.8°F, respiratory rate 16/min, pulse 100/min, and blood pressure 110/70 mm Hg. Auscultation of the heart revealed no murmurs. The lungs were clear. Abdominal examination showed right lower quadrant tenderness without rebound; no hepatosplenomegaly was present. On pelvic examination there was a thick yellowish vaginal secretion with right adnexal tenderness and no masses. Neurologic examination was nonfocal. The hemoglobin was 10.7 grams and the leukocyte count was 36,200/mm^3 with 33% neutrophils, 13% band forms, 10% lymphocytes, 31% atypical monocytes, 6% metamyelocytes, 5% myelocytes and 2% atypical lymphocytes.

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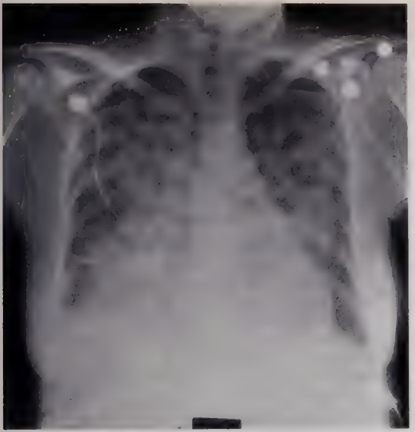

Fig. 1. Chest radiograph prior to intubation showed diffuse, fluffy pulmonary infiltrates.

Shortly after admission, the patient complained of increasing shortness of breath. Repeat examination disclosed tachypnea with a respiratory rate of 32/min. An arterial blood gas determination on room air revealed pH of 7.40, pCO_2 of 29 mmHg, and pO_2 of 40 mmHg. The chest radiograph showed diffuse bilateral interstitial and alveolar infiltrates (Fig. 1).

The patient was nasally intubated and treated by mechanical ventilation with positive end-expiratory pressure. The pulmonary capillary wedge pressure was 12 mmHg and the static pulmonary compliance measured from the ventilator was 0.032 L/cm H_2O. Fiberoptic bronchoscopy showed no endobronchial lesions, inflammation, or visible bleeding. Selective bacterial cultures and bronchoalveolar lavage (20 ml aliquots of normal saline ×5) were obtained. A 72-ml return of BAL, blood-tinged, was collected from the right middle lobe. After centrifugation the differential cell count showed 15% lymphocytes, 45% neutrophils, and 55% highly atypical monocytoid cells with erythrophagocytosis which were identical to cells present on a bone marrow aspirate and biopsy performed the same day as the BAL. The bone marrow study was consistent with the diagnosis of malignant histiocytosis (Fig. 2). Examination of the BAL smears as well as special stains and cultures for microorganisms were all negative. Viral serologic studies were also negative. Cultures from blood, urine, and cervix showed no growth.

The patient was treated with cyclophospha-

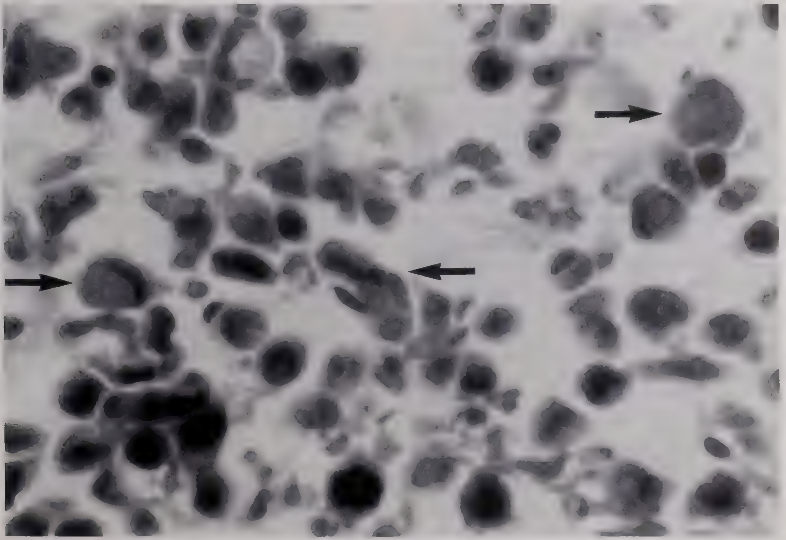

Fig. 2. Bone marrow with atypical histiocytes and prominent erythrophagocytosis (arrows) (H&E original magnification ×1000).

mide, bleomycin, doxorubicine, vincristine, and dexamethasone, followed by methotrexate and leucovorin. Despite a stormy initial course, she improved clinically and radiographically and was extubated after 23 days. BAL just prior to extubation was clear and showed a differential cell count of 84% macrophages, 10% lymphocytes, and 6% neutrophils. Postextubation spirometry was consistent with mild restriction (vital capacity 1.00 L [61% predicted]; total lung capacity 3.71 L [83%]; FEV_1/FVC, 88%).

Discussion. This patient with malignant histiocytosis had an unusual presentation, since the adult respiratory distress syndrome dominated the clinical picture. In reviewing the literature, we were unable to find any case in which bronchoalveolar lavage was used to establish the pulmonary involvement of malignant histiocytosis, which often evades antemortem diagnosis (5). To what extent the patient's ARDS picture was due to malignant infiltration vs. intraalveolar hemorrhage is impossible to establish, since both these processes showed significant resolution on the repeat BAL.

Bronchoalveolar lavage is a formidable research tool in interstitial lung diseases (8) and ARDS (9, 10). It is also extremely useful in rapidly establishing the diagnosis of diffuse infiltrates in the immunocompromised host (11) where pulmonary edema, infections, drug reactions, pulmonary hemorrhage, or malignant infiltration can be difficult to differentiate clinically. Indeed, BAL proved to be very helpful in the present case, both in the initial management and in follow-up.

Rapid diagnosis of this disorder is critical, since combined chemotherapy significantly improves survival (4, 12). The pulmonary manifestations are particularly sensitive to chemotherapy (6), as reflected in the present case, in which the patient was successfully weaned from mechanical ventilation and only demonstrated mild restrictive changes in pulmonary function testing after remission. Although the findings on bronchoalveolar lavage are not pathognomonic of malignant histiocytosis, the technique allowed rapid differentiation of the many causes of ARDS in this patient and therefore expedited definitive treatment.

Acknowledgments

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Clear-Cell Mucoepidermoid Carcinoma Arising in the Nasal Cavity:

Case Report with Ultrastructural Observations

BERNARD PEISON, M.D., BARRY BENISCH, M.D., IRA S. SCHWARTZ, M.D., AND RONALD E. GORDON, PH.D.

Abstract

The authors report an unusual clear-cell variant of mucoepidermoid carcinoma of minor salivary gland origin arising in the right posterior aspect of the nasal septum of a 52-year-old woman. Histochemical stains revealed the presence of epithelial mucin, and ultrastructural study disclosed numerous desmosomes and cytoplasmic tonofilament bundles, permitting the designation of mucoepidermoid carcinoma. The relevant literature is reviewed.

Case Report. A 52-year-old woman was admitted to the hospital because of bifrontal headaches and right-sided nasal polyps causing obstruction. Physical examination was essentially negative, except for the presence of friable polypoid tissue originating under the right middle turbinate posteriorly. Laboratory findings, including chest and multichannel blood chemistry studies, were normal. Abdominal computed tomography (CT) scan showed no abnormality. X-rays of the nasal sinuses revealed destructive osseous changes in the posterior portion of the sella turcica. CT scan of the head showed a large, irregular, midline soft-tissue mass filling the right sphenoid sinus, with partial destruction of the nasal septum and sella turcica (Fig. 1). A biopsy specimen was obtained. The patient was transferred to another hospital, where she underwent a right lateral rhinotomy with excision of tumor which appeared to arise from the posterior nasal septum. Her condition remained stable for 11 months, at which time a CT scan of the nasal sinuses revealed recurrent tumor in the left nasal cavity. She received neutron beam therapy at another facility for a total dose of 2,043 neutron rads over a period of one month.

Pathologic Findings. The respiratory mucosa was diffusely infiltrated by solid nests of tumor cells displaying small, dark nuclei and clear cytoplasm (Fig. 2). Mucicarmine and PAS stains with and without diastase pretreatment showed intercellular mucin deposits; the cytoplasm of the clear cells remained unstained by these procedures (Fig. 3). Acinar structures with intraluminal mucin were also evident (Fig. 4).

Ultrastructural study was performed on tissue fragments from 10% buffered formalin postfixed in 3% glutaraldehyde containing 0.2 M sodium cacodylate buffered at pH 7.3. The tissue was washed, treated with cacodylate-buffered 1% osmium tetroxide, dehydrated in ethanol, and embedded in Epon 812. Representative areas were selected from 1-μ sections stained with methylene blue and azure II. At low-magnification electron microscopy, the tumor comprised a nearly homogenous population of cells forming large nests. Most cells were polarized with a mi-

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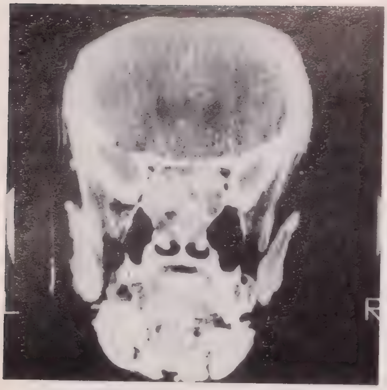
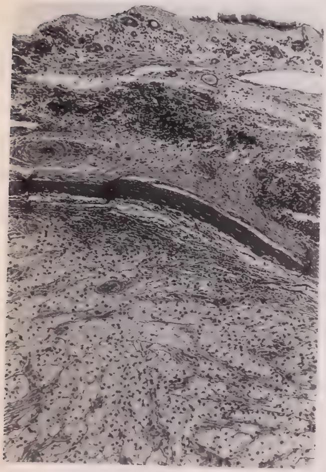
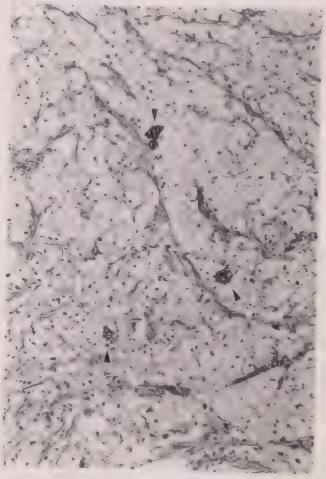


Fig. 1. Frontal computed tomographic scan. Large midline mass obliterates nasal cavities, septum, and portions of sphenoid sinuses.

crovillous luminal surface and basal lamina at the opposite pole. All cells were linked to their neighbors by desmosomes and contained large pools of glycogen. Some showed many tonofilament bundles, while others exhibited stacked granular endoplasmic reticulum. A few cells adjacent to lumens also contained membrane-bound, electron-dense, secretory-type granules (Fig. 5).

Discussion. Malignant neoplasms of the nose and paranasal sinuses comprise approximately 15% of all cancers of the upper respiratory tract (1). Squamous-cell carcinomas represent 80%–90% of these tumors (2), with 4%–8% being of minor salivary gland origin (3). In the latter group, adenoid cystic carcinoma is the most common variety, followed by adenocarcinoma, malignant pleomorphic adenoma, and mucoepidermoid carcinoma (4). It is difficult to determine the precise number of cases of minor salivary gland mucoepidermoid carcinomas reported in the literature; several authors have classified





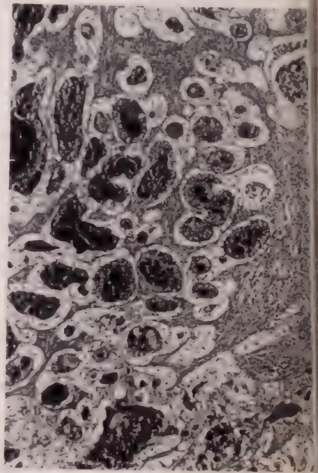


Fig. 2. Left Low-magnification photomicrograph of tumor with overlying respiratory mucosa. Solid pattern of clear cells compresses adja-cent bone (hematoxylin-eosin, original magnification ×40). **Fig. 3. Middle** Focal mucin deposits (arrows) among tumor cells with clear cytoplasm (diastase-PAS stain, original magnification ×100). **Fig. 4. Right** Area of tumor comprising clear cells in tubular arrangement with intraluminal mucin (diastase-PAS stain, original magnification ×100).

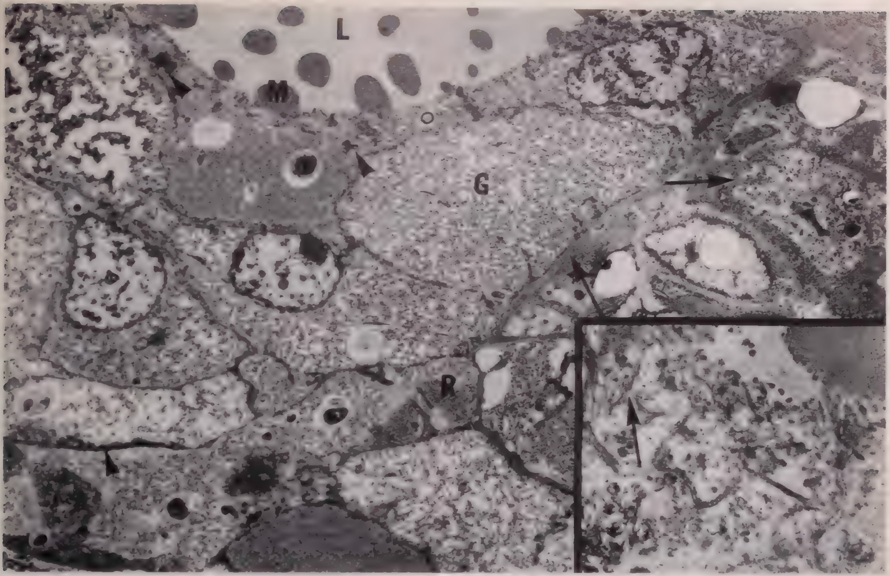


Fig. 5. Low-magnification electron micrograph, showing several cells and cell processes. Lumen (L) contains mucinlike material (M). Collagenous basement membrane outlines some cells (arrows). Cytoplasm contains abundant glycogen (G); some cells show granular endoplasmic reticulum (R). Desmosomal attachments are evident (arrowheads). Inset shows tonofilament bundles (arrow) and desmosomes (uarnyl acetate and lead citrate stain, original magnification ×3,360; inset, original magnification ×12,000).

them collectively as minor salivary gland tumors rather than considering individually the histologic types.

Mucoepidermoid carcinoma was first described as a distinct tumor of the salivary glands by Stewart and associates, in 1945 (5). The origin of this tumor is probably from the large ducts of both major and minor salivary glands. It comprises approximately 6%–8% of all salivary gland tumors (5). Three cell types may be recognized: a mucin-producing cell, an epidermoid (squamous) cell, and an intermediate or basal cell. The latter may differentiate into the other two cell types. The tumor may produce cystic or glandular strucures, solid nests, or various combinations of these patterns. A review of 815 cases of mucoepidermoid carcinoma by Eversole showed that the parotid gland was the most commonly affected major salivary gland (6). The palate was the most common location for minor salivary gland mucoepidermoid carcinomas, accounting for 41.1% of intraoral tumors of this type. Histologically and biologically, mucoepidermoid carcinoma has been classified into low, intermediate, and high grades (7). The 10-year cure rate for those of minor salivary gland origin at all sites is 78.6% for low-grade and only 50% for high-grade lesions (8). The most important factors in the prognosis of these tumors are the degree of histologic differentiation and the presence or absence of tumor at the surgical margins of the resected specimen.

Mucoepidermoid carcinoma of the minor salivary glands has a tendency to cause bone remodeling rather than aggressive bone destruction (9). This was evidenced by the case reported by Schaeffer et al (10), in which the tumor widened the posterior nasal vault and ethmoid complex with little, if any, marginal bone destruction. In our case, however, the tumor produced extensive bony destruction of the nasal septum and sella turcica. The mucinous tumor cells may rupture and release their content into the tumor stroma, with focal cyst formation.

The etiologic factors responsible for the development of all types of minor salivary gland neoplasms remain obscure. A significant relationship between nasal and paranasal carcinomas and occupation is shown by the increased risk of ethmoid adenocarcinoma in hard-wood furniture workers (11). Acheson et al (12) regard the offending agent to be related to wood dust rather than to polishes, lacquers, or varnishes. One report documents a mucoepidermoid carcinoma developing in a 7-year-old girl 2 years after the impaction of a button in her nose (8). Schaeffer and colleagues' patient had a posterior nasal cavity mucoepidermoid carcinoma that obstructed the sphenoid sinuses, causing bilateral secondary sphenoid sinus mucoceles (10). Gamez-Araujo et al (13) described 18 patients with mucinous adenocarcinomas of the nose and/or paranasal sinuses. Thirteen patients had tumors in the paranasal sinuses, and the nasal cavity was the site of origin in five patients. Three of these tumors showed diffuse sheets of large round cells with abundant cytoplasm, producing a "signet-ring-cell" appearnce. In other areas, the tumors assumed a clear-cell character, as seen in renal adenocarcinoma (hypernephroma), but were distinguished by the demonstration of mucin production. Bone involvement was observed in all but 2 of the 18 patients. Adenocarcinoma of the clear-cell type displaying an acinar or solid pattern should alert the pathologist to the possibility of a metastasis from an occult renal adenocarcinoma. Histochemical studies to differentiate mucin and glycogen as well as renal imaging studies are mandatory to such cases. Renal adenocarcinoma contains glycogen and is mucin-negative. Batsakis and McBurney (14) refer to renal carcinoma as the tumor most frequently giving rise to metastases to the nose and paranasal sinuses.

The nasal mucoepidermoid carcinoma described here is a clear-cell variant, the true nature of which was revealed by appropriate histochemical and ultrastructural studies.

Acknowledgments

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Student Corner

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Tuberculosis and Breast Cancer: Case Report and Review

AMY GOLDBERG, M.D.

Immunodeficiency is a phenomenon commonly associated with cancer, affecting both the cell-mediated and the humoral arms of the immune response (1). Studies of immune function in patients with advanced cancer have shown impairment (2–4). It is not yet clear whether host immune depression precedes or follows the development of the cancer. Probably more important is to ascertain whether host immune depression is related to the extent of spread and subsequent behavior of the cancer. It may be hypothesized that reversal of this immunosuppression may subsequently lead to longer durations of remission and survival.

Calmette and Guerin successfully developed an attenuated strain of mycobacterium bovis, Bacillus Calmette Guerin (BCG), which has been used as a vaccine in the prevention of human tuberculosis (5). A wide variety of immunologic effects of BCG preparations have been reported, including alterations of antibody production, changes in delayed hypersensitivity responses, and altered macrophage function (6). Several clinical trials have suggested value for BCG preparations in the treatment of human cancer, either as a single modality or in combination with chemotherapy (7–10).

MER, the methanol extraction residue of BCG, is a nonviable nonspecific potent immunostimulant. In a variety of animal models it has been shown to activate the reticuloendothelial system, to accelerate the rate of particle clearance from the blood, to induce cytotoxicity activity against target cells, and to augment both cell-mediated and humoral immunity (11).

The role of prior tuberculosis, prophylactic BCG vaccination, chemoimmunotherapy with BCG or MER has been investigated extensively with the aim of prolonging survival and increasing the disease-free interval in various neoplasms.

Case Report

A 60-year-old black woman noticed a mass in her left breast just above the nipple. She had an early onset of menarche and a late menopause. She was a nulli-gravida and had not been exposed to estrogens. Previous needle biopsy of the breast lesion was benign. Medical history was significant for treatment of tuberculosis eight years ago.

Physical examination revealed a firm nontender 2 × 3 cm mass above the nipple of the left breast.

The patient had excisional biopsy of the lesion which revealed invasive carcinoma that was treated with modified radical mastectomy. Histologically the carcinoma was poorly differentiated with focal lobular differentiation. Intraductal carcinoma was present in the three other quadrants. Seventeen regional nodes were negative for tumor, but noncasseating epithelioid cell granulomata were present in some of the nodes. Estrogen and progesterone receptor proteins were positive.

Literature Review and Discussion

Until recently, size of tumor and nodal involvement were the classic and sole criteria used for staging prognosis and for devising protocols for treatment. However, several studies of prognostication on the basis of lymphatic invasion, blood-vessel invasion, and estrogen receptor status are now available (12). Several investigators have studied the prognostic significance of

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the immunocompetence of cancer patients determined at diagnosis prior to treatment. It is possible that the qualitative and quantitative responsiveness of the immune system in a patient with breast cancer may be related to the ultimate prognosis (4, 12–17).

It has been shown in the human breast cancer model that the presence of neoplasia is accompanied by distinctive alterations in the immune system of the host: manifestations of in situ antitumor response on the one hand (18), and depression of cell-mediated immune function on the other (19). Manifestations of antitumor activity involve macrophages, natural killer cells, and humoral factors. Though not specifically induced by tumor, these spontaneous responses can cause selective tumor-cell killing. A tumor-restraining force of this kind draws its resources from various components of the host's immune system. Levels of cell-mediated immunity may thus, directly or indirectly, reflect the potential for impeding the neoplastic process (17).

Many investigators have been able to show evidence of immune impairment related to breast cancer by criteria of cell-mediated immunity, such as cutaneous responses to recall antigens, de novo sensitization by contact sensitizing agents, lymphoproliferative responses to mitogens, antigens, or alloantigens, and proportion of E-rosette forming cells (2–4). The crucial question in studies of general immune competence in cancer patients is whether immune competence can be shown to correlate with diagnosis, extent of disease, or response to treatment in the individual patient.

Relationship of Immunocompetence to Cancer and Prognosis. Bolton et al. (2) found no significant difference between "early" breast cancer and control patients, or between cancer stages in peripheral lymphocyte count, serum immunoglobulin levels, lymphocyte response to phytohemagglutinins (PHA), or Mantoux response. Age was found to have a crucial effect on some of these parameters, and some apparent differences between the various groups lost significance after appropriate allowances were made for age. However, important differences were seen with the dinitrochlorobenzene (DNCB) skin test, which measures ability to become sensitized to an antigen as well as to mount a delayed hypersensitivity response. Therefore, this test should give more complete information than delayed hypersensitivity responses to recall antigens where the presence and degree of antigen exposure are unknown. Responses to DNCB were significantly depressed in patients with "early" breast cancer compared to controls. Patients with disseminated cancer showed greater depression than "early" breast cancer patients. These differences persisted after allowing for age effects.

Adler et al. (3) used an integrated score of immune function comprising four functional parameters (in vivo response to Purified Protein Derivative (PPD) and DNCB and in vitro lymphocyte stimulation by PPD and PHA) to express the comprehensive level of immunocompetence of each patient. Fifty-one percent of the patients with early operable tumors were shown to be at least partially immunosuppressed. This proportion rises to 68% of inoperable and 89% of metastatic patients. Only 11% of the controls were immunosuppressed. These authors concluded that an impairment of immune function measured by these parameters of cell-mediated immunity is associated with the presence of breast cancer.

It was often demonstrated, using one or another of these four tests, that patients with breast cancer have impaired immune function and that progressive impairment occurs as the tumor burden increases (2–4). Relatively few studies have examined the relationship of immune function to prognostic criteria. The aim of these studies was to demonstrate whether immune reactivity correlates with the extent of disease in carefully staged patients with breast cancer and to determine whether, within stages, immune reactivity correlates with prognosis.

In the early studies, patients with positive skin-test reaction to DNCB at the time of definitive surgery for resectable neoplasms showed a significant decrease in short-term recurrence rate when compared with patients with a negative DNCB response (13). After longer follow-up, it was demonstrated that in cancer patients in general, DNCB reactivity correlates with long-term recurrence and survival rates (14). Cunningham (15) reported in 1976 that patients with recurrent breast cancer treated with chemo- or hormone therapy survive longer if they can mount a response to DNCB before treatment.

Snell (16) retrospectively studied 102 patients with inoperable bronchial cancer who had tuberculin tests at the time of diagnosis. They were followed up to see if there was any correlation between degree of tuberculin reactivity and subsequent survival. There was a significant difference in survival between positive and negative tuberculin reactors; the former had a median survival time almost twice that of the latter. These results showed that positive tuberculin reactivity carried a substantial advantage in survival time in this group of patients. Tuberculin testing may be useful in helping to assess prognosis in patients with inoperable bronchial tumors.

However, possible flaws in study design may have accounted for these results. First, the positive and negative groups may not have been comparable clinically; second, previous exposure to tuberculosis may convey an advantage in survival in patients subsequently developing bronchial carcinoma. Third, positive tuberculin reactivity is being used in this situation as a nonspecific indicator of an intact cell-mediated immune system, thereby implying a good host response against malignant cells in these patients. However, some negative reactors may have good cell-mediated immunity but happen never to have been sensitized to mycobacterial antigens. Testing with a more universally experienced antigen might have given more clearly defined results.

The relationship of immune reactivity to the stage of disease and to prognosis within stages was studied in 202 women with breast cancer (4). Krown et al. found a significant decreasing trend of DNCB reactivity with extent of disease. No significant difference in recurrence distribution was seen when all primary operable breast cancer patients with positive and negative DNCB responses were compared. When the survival distributions for all DNCB positive and negative patients were compared, the DNCB-positive patients showed a significantly longer survival. However, when the survival distributions for DNCB positive and negative patients with either primary operable or advanced breast cancer were compared separately, significant differences were not seen. Krown et al (4) concluded that although DNCB reactivity is progressively impaired in patients with increasing tumor burden and correlates with survival in general, it did not provide prognostically important information over that derived from careful clinical and pathologic staging.

Adler et al. (2, 17) put forth the hypothesis that two different types of immunosuppression exist in breast cancer patients: a primary patient-related and a secondary tumor-related immunosuppression. The degree to which patients' immune capacity is able to withstand secondary tumor-induced immunosuppression appears to be closely related to favorable or unfavorable evolution of disease. To those breast cancer patients whose tumor is surgically curable, secondary tumor-related immunosuppression is irrelevant. However, it appears to be of utmost importance for the clinical well being and survival of the bulk of all breast cancer patients with occult disease. Adler et al presumed that the influence of the patient's immune capacity on the development of their neoplastic disease could be reflected in prognosis by the application of immunologic criteria used in previous investigations. Their goal was to devise further prognostic separation within each of the first two stages of breast cancer based on responses to measures of cell-mediated immunity. In their study, prognosis was analyzed in terms of incidence of recurrence and length of disease-free interval in operable breast cancer and in terms of length of survival with disease in metastatic patients (17).

Their results illustrate a definite inverse relationship between immunity and probability of recurrence. When the entire operable patient group (stage I and II) is subdivided into optimal and suboptimal responders according to initial score of immunocompetence, they fall into two separate prognostic ranges (optimal responders −0.26 probability of recurrence; suboptimal responders −0.60 probability of recurrence). When optimal and suboptimal responders are similarly distributed among stage I and II patients, alterations in probability of recurrence are seen.

Stages I patients with concomitant high immmune function had a probability of disease recurrence as low as 0.06, as compared to all stage I patients (0.22) and stage I patients with low immune function (0.41). This clearly implies an additive prognostic effect of stage and immunity. The opposite was shown for stage II patients with low immunity (all stage II 0.64, optimal 0.45, suboptimal 0.79). In those instances where nodal stage and level of immunity are of opposed prognostic impact, such as stage I patients with low and stage II patients with high immune capacity, the effect of one appears to modify that of the other. In this setting, good immunocompetence is found to improve the prognosis within stage II beyond that of the entire group (0.64–0.45), whereas within stage I, poor immunity depressed the patients' prognosis below that of the entire group (0.22–0.41).

The data presented in this article show a significant degree of prognostic separation of all operable breast cancer patients by application of immunologic criteria. Further segregation was achieved by applying conventional staging coupled with immunologic substaging into optimal and suboptimal responders. These findings allow further prognostic allocation of "high risk" cancer within each stage, thereby narrowing the range of an otherwise wide state of disease. This may represent a guideline for selecting patients for postoperative adjuvant chemotherapy and immunotherapy.

Mandeville et al. (12) report the value of several cell-mediated immunologic assays in the evaluation of the patients' immune competence in relation to predicting the disease-free survival or the likelihood of recurrence. Their results indicate that at diagnosis, blastogenic responses of lymphocytes to phytohemagglutinins (PHA) and concanavalin A (Con A) and hypersensivity reactions to recall skin antigens are related to stage of disease, whereas only lowered responses to PHA and recall antigens are related to five-year disease-free survival. Results clearly indicate that patients who are capable of displaying delayed cutaneous hypersensitivity to recall antigens or who show a normal lymphocyte response to PHA have a better chance of surviving five years than those who do not respond to these tests. Responses to recall antigens in vivo and to PHA in vitro could thus be used as biological markers of disease evolution in breast cancer patients, and are useful tools in predicting prognosis even in the earlier stages of the disease.

These studies point to an early and persistent immune impairment in patients with breast cancer and suggest a close correlation between immune competence, tumor burden, and prognosis in these patients. As Adler et al. (17) demonstrated, stage I and II breast cancer is a very heterogeneous group; however, oncologists may be able to discriminate a subgroup of patients with higher risk of recurrence based on analysis of immunocompetence.

Use of BCG/MER in Cancer Treatment. When evaluated in animals, BCG was found to have a favorable effect on leukemia and several other tumors. The results ultimately led to epidemiologic studies designed to assess whether BCG vaccination could prevent cancer in humans (20).

After it was demonstrated that MER had antitumor activity alone or in combination with surgery, radiation, or chemotherapy in a variety of animal tumor models, a standardized preparation of MER was prepared and introduced into clinical trials in the treatment of patients with advanced cancer (21).

Alberts et al. (7) studied the effect of adding Bacillus Calmette-Guerin (BCG) to a standard chemotherapy regimen of doxorubicin (Adriamycin) and cyclophosphamide (A-C) for the treatment of Stage III and IV ovarian carcinoma. One hundred and fifty-four patients with no prior chemotherapy and measurable disease were randomly assigned to receive A-C or A-C and BCG. Patients were evenly distributed between the two groups with respect to histologic tumor types and grades. The results indicate that the addition of BCG to standard A-C treatment for advanced ovarian carcinoma appears to have increased response rates as well as overall length of survival.

When O'Connell et al. (22) added BCG to the treatment of patients with metastatic cancer, a different result followed. One hundred and thirty adult patients with metastatic solid tumors were studied to evaluate the therapeutic results and immunological effects of BCG treatment. It was not possible to demonstrate any significant clinical or immunologic benefit from BCG administration in this patient population with the methodology employed. Possibly more subtle differences could have been demonstrated in patients with an earlier stage of disease.

Robinson et al. (8) believe that there are two main reasons for using immunotherapy combined with radiochemotherapy: first to reverse the immunosuppression after radiochemotherapy, and second to augment the capacity of the immunologic system to destroy residual tumor. In their study, patients with Dukes' B and C colorectal cancer were randomized to adjuvant therapy after radical surgery. One group was treated with chemotherapy in combination with radiotherapy (RC). The second group was treated by chemotherapy with radiotherapy plus MER/BCG (RCM). In patients with Dukes' C disease, the survival at 54 mo and the disease-free interval up to 24 mo were significantly better in the RCM than in the RC subgroups. There was no significant difference in the survival and disease-free interval between RC- and RCM-treated patients with Dukes' B disease. It is too early to assess whether their treatment merely delays recurrence and increases survival in Dukes' C colorectal cancer or whether it actually increases the cure rate. The results of this study have confirmed the value of MER in adjuvant therapy of patients with Dukes' C colorectal cancer. On the other hand, no apparent therapeutic effect of MER was found in patients with Dukes' B rectosigmoid cancer. It could be hypothesized that a certain tumor burden is needed before MER treatment is effective and over which MER is ineffective.

Recently, Hersh et al. (21) reviewed 41 clinical trials of MER therapy involving approximately 3,000 patients with malignant disease. The diagnoses included lung, colon, and breast cancer, malignant melanoma, acute leukemia, and a small number of other malignancies. MER has been used as an adjuvant to therapy for advanced disease and as prophylaxis against recurrence after surgery. Most studies have used the intradermal route but subcutaneous, intralesional and intravenous routes have also been explored.

Little activity has been observed with the intradermal route. There is no confirmed example of an increased remission rate, remission duration, or survival induced by MER therapy. When given by the intralesional route, MER can cause regression of metastatic malignant melanoma nodules. When given by the intravenous route, MER is a potent immunoadjuvant. Antibody-dependent cellular cytotoxicity and natural killer cell activity were both boosted, and effector lymphocyte and effector monocyte functions were both activated. These authors concluded that the future of therapy with mycobacterial fraction awaits the development of more potent, less toxic fractions that can be administered systemically.

In a study by Hortobagyi et al. (9), 105 patients with metastatic breast cancer were treated with 5-fluorouracil, doxorubicin, cyclophosphamide, and BCG (FAC-BCG). The results were compared to those observed in a group of 44 patients treated with FAC chemotherapy alone.

Although the overall response rates were similar, the duration of remission was 9 mo for FAC and 14 mo for FAC-BCG. Similarly, survival of responding patients treated with FAC-BCG was significantly longer (24 mo) than that in the chemotherapy alone treated group (15 mo). Nonspecific immunotherapy with BCG appears to prolong duration of remission and survival for responding patients.

However, the FAC-BCG treated group contained a somewhat higher percentage of patients with predominately soft tissue and bone disease and consequently a somewhat lower fraction of patients with visceral disease. This might have favored the FAC-BCG group, since these authors' analysis showed that patients with soft tissue and bone disease survive significantly longer than patients with visceral metastases.

In a prospective trial, Muss et al. (23) studied the addition of MER as nonspecific immunotherapy to two combination chemotherapy programs in patients with metastatic breast cancer, and found that it did not enhance response rate, duration of response, or survival.

In another study by Hortobagyi et al. (10), 52 patients with locally advanced primary breast cancer without distant metastases were treated with three cycles of combination chemotherapy: FAC-BCG, followed by local therapy and adjuvant chemotherapy to complete two years of treatment. The complete remission rate with this multimodal approach is high, and long-term disease-free survival is achieved in a considerable number of patients; 84% of the patients achieved a complete or partial response after three courses of chemotherapy, and 94% were rendered free of disease with subsequent local therapy. This degree of tumor reduction allowed tumors to become technically operable.

Buzdar et al. (24), in a prospective randomized trial to determine the role of BCG in the treatment of patients with operable breast cancer conducted between May 1977 and April 1980, 238 patients treated with fluorouracil, doxorubicin, and cyclophosphamide (FAC) chemotherapy, but patients were randomized with and without BCG vaccine. In 1984 no significant differences were found in disease-free survival of patients treated with FAC alone and those treated with FAC-BCG.

Hubay et al. (25) reported, in a prospective randomized clinical trial of adjuvant treatment of 312 stage II breast cancer patients by chemotherapy, antiestrogen therapy, and immunotherapy, that the addition of nonspecific immunotherapy with BCG had no effect on disease-free survival. However, the median follow-up time was 41.3 mo.

Does Prior Tuberculosis Protect Against Cancer? Some of the cited studies conclude that BCG/MER is an immunostimulant and thus can be used to reverse the immunosuppression of cancer. Therefore, if BCG has been relatively successful in treating cancer, could previous tuberculosis incur a protective effect? Ezra Greenspan (26–28) noticed two patients with bulky stage IIIB ovarian cancer were found to be apparently cured 9 and 14 years after thiopeta-plus-methotrexate treatment given in the 1960s. Both had sustained extensive pulmonary and systemic tuberculosis as young women 11 and 15 years prior to the onset of ovarian cancer. This observation led him to a retrospective analysis of 600 patients with disseminated breast and ovarian carcinoma treated with chemotherapy from 1954 to 1974 (26). Forty-two (7%) were long-term (5–20 years) survivors. Seventy-five percent of these survivors had an unusual incidence of extensive previous tuberculosis, abnormal chest x-ray, and positive tuberculin tests; only 25% of the survivors had negative PPD tests with normal chest x-rays. He concluded that previous tuberculosis in women with breast and ovarian carcinoma may play a role in unusually good long-term responses to chemotherapy, yielding unexpected long-term disease-free survival or cure.

In further review of Bolton et al. and Krown et al., Greenspan (26) noted that PPD positivity is greater in patients with large bulky primary T3 tumors than in those with small tumors, whether or not nodes are positive. Immunocytologists might deduce that previous tuberculosis acts to recall, facilitate, or trigger favorable macrophage, lymphocyte, and cellular humoral mechanisms during a chemotherapy-induced release of tumor antigens during the tumor kill process (26). A hypothesis could be offered that previous tuberculosis delays but does not prevent the onset of cancer, and thus could lead to an indolent clinical course. Greenspan even suggests that lack of tuberculosis should probably be added to nutritional, hormonal, and other environmental factors that may relate to breast cancer. If this concept is valid, repeated BCG immunization may be warranted in young women, particularly those from high-risk breast cancer families.

In the case presented, the patient appears to have a bulky primary breast carcinoma without apparent nodal involvement. Could her previous tuberculosis have led to an indolent clinical course? It is certainly possible, and follow-up would be necessary as well as very interesting.

The possible protective effect of tuberculosis against cancer, together with the known immune-stimulating properties of BCG, motivated Clemens and Stanton to evaluate 14 studies of BCG prophylaxis against varying cancers (19). Of these 14 studies, 3 found high levels of protection, 8 found no effect, and 3 suggested that BCG may actually raise the risk of cancer. They concluded through methodologic evaluation that none of the 14 studies of BCG prophylaxis against cancer exhibited sufficient strength to permit conclusions about the role of BCG in preventing cancer.

Summary and Conclusions. If prolonged survival from cancer is favorably influenced by prior tuberculosis and BCG, then a fresh look should be taken at BCG chemoimmunotherapy as potential prophylaxis and treatment. However, not until greater experimental evidence from randomized trials indicates its benefit will it become part of standard treatment. Dosing schedules, mode of administration, type of preparation, and type of cancer are only a few parameters that need to be further evaluated before BCG or MER become part of a standard chemoimmunotherapy regimen.

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Wandering Spleen: Case Report and Review

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Anomalies of the peritoneal duplications ("ligaments") which normally support and limit the mobility of the spleen can allow the organ to become displaced from its usual position in the left hypochondrium. This condition is characterized by abnormal position and enhanced mobility of the organ, which is determined primarily by the length of pedicle containing the splenic vessels and termed wandering spleen. Other descriptive terms have included floating, aberrant, prolapsed, displaced, drifting, ectopic, ptotic, and dystopic spleen (1–3). However, "wandering" spleen is the term most frequently used, and it serves to distinguish this condition from splenosis or accessory spleens. Litten (4) and Maingot (5) suggest the term "dislocated" spleen be reserved for fixation of a wandering spleen in an abnormal position.

This report describes a case of wandering spleen in which the patient's initial symptom was an acute abdomen after dislocation to the pelvis. A brief overview of the literature is presented in an attempt to provide a perspective on the clinical manifestations, diagnosis, and associated morbidity of this rare but interesting condition.

Case Report

A 22-year-old black woman (gravida 2, para 1, abortus 1) was admitted to The Mount Sinai Hospital with a two-week history of episodic diffuse abdominal pain, loss of appetite, and weight loss of 15 lb. For the six days prior to admission, she experienced increasing nausea and vomiting, intermittent fever up to 102.5°F and increasing urinary frequency and dysuria. No changes in bowel habits were noted over the two weeks. Her last menstrual period was one week prior to admission, of regular duration but atypically scant. There was no history of pelvic inflammatory disease, urinary tract infection, or any venereal disease in herself or her partner.

The obstetric history included an elective, first trimester abortion four years previously and a cesarean section ten months prior to admission. A routine postnatal physical examination at six weeks revealed an asymptomatic abdominal mass in the left lower quadrant of approximately 9 × 5 × 5 cm. After ultrasonography and liver-spleen scanning with ^{99m}Tc-sulfur colloid, the mass was diagnosed as a wandering spleen.

Physical examination revealed a slender, anxious woman in acute abdominal distress. The temperature was 99.4°F, respirations 18/min, pulse 100/min supine, 124/min standing, blood pressure 90/60 mmHg supine, 70/50 mmHg standing. Bowel sounds were diminished; a fixed, exquisitely tender 8-cm wide mass extended 10 cm superiorly from the symphysis and was dull to percussion. Diffuse tenderness, guarding, and rebound tenderness was noted, the latter greatest in the right lower quadrant. There was no costovertebral angle tenderness. Pelvic exam revealed a scant, yellowish vaginal discharge, right adnexal fullness, and exquisite tenderness upon cervical motion.

Laboratory findings were as follows: hemoglobin 12.5 g/dl; hematocrit 38%; white cell count 14,000/mm^3 with 4% bands; alkaline phosphatase 114 IU/1: total bilirubin 1.3 mg/dl; amylase 84 U/ml; erythrocyte sedimentation rate 40 mm/hr. Urinalysis yielded a specific gravity of 1.035 with 20–30 white blood cells per high power field and 4+ bacteruria.

On plain abdominal x-ray (Fig. 1) there was a pelvic shadow of soft tissue density extending superiorly in a semicircular shape with its apex

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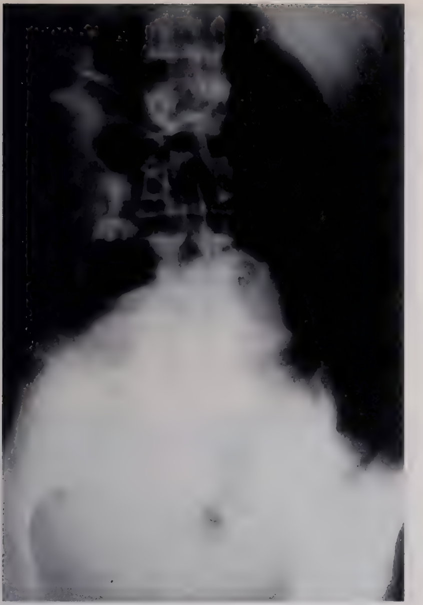

Fig. 1. KUB film on admission. In addition to pelvic shadow of soft tissue density, dilated loops of small bowel with several air-fluid levels and loops of small bowel extending high into the left upper quadrant are evident.

at the level of the fourth lumbar vertebra, dilatation of small bowel with several air-fluid levels and loops of small bowel, but no splenic shadow, in the left upper quadrant. Liver spleen scan using ^{99m}Tc-sulfur colloid showed a normally sized liver but failed to visualize the spleen. Computed tomography of the abdomen and pelvis (Fig. 2) confirmed a pelvic mass of soft tissue density with regions of decreased attenuation.

At surgery, a grossly enlarged spleen (8 × 12 × 18 cm) was found immediately beneath the abdominal wall following a midline infraumbilical incision (Fig. 3). After mobilizing the spleen from adhesions to the bladder, uterus and appendix, a splenic pedicle of 10 cm length was noted with four complete revolutions of dextrotorsion. The pedicle was traced to its origin at the celiac trunk, but did not contain the tail of the pancreas. There were no splenorenal or gastrosplenic ligaments (including gastric vessels) present. Following detorsion of the splenic pedicle (Fig. 4), thrombi in the splenic vessels could be palpated distal to the constriction caused by its torsion. The pedicle was ligated and transected proximal to the constriction and an appendectomy was performed on an inflamed, hyperemic appendix which had been stretched upwards anterior to the cecum. Dissection of the 1000 gm spleen revealed thromboses of both splenic arteries and veins and severe parenchymal congestion (Fig. 5).

The postoperative course was uneventful, and the patient was released six days after splenectomy.

Discussion

Historical Background. Hippocrates, Pliny, Herophilus, and Galen all recognized that the spleen could be located in unusual positions (6–8). The earliest clinical description of a wandering spleen confirmed by autopsy is attributed to a Dutch physician, Van Horne, in 1667 (9).

Surgery of the spleen was a major part of the early history of abdominal surgery, and wandering spleen was one of the earliest indications for splenectomy (1, 10–12). Although Collier (13) has attributed the first splenectomy for a wandering spleen to Urbinato in 1873, the first published report was about a procedure performed in 1877, by Martin (14); the patient successfully recovered. The first cases of splenopexy for wandering spleen were performed in 1882 by Tuffier (14, 15) and by Rydygier (2, 12) but were not reported in the literature until 1895 (2, 16). By 1926, there were at least five different procedures for splenopexy performed (2). With advances in surgical technique and management, and the development of an effective pneumococcal vaccine, splenectomy became the treatment of choice for wandering spleen. As of 1980, approximately 350 reports had been published in the world literature (5).

Prevalence and Clinical Presentation. Although prevalence or incidence rates for wandering spleen cannot be accurately estimated for the general population, the rarity of the condition is evident from its infrequent occurrence (0.2%–0.3%) among large groups of patients undergoing splenectomy (17, 18). Of 1,437 patients at a combined medical-surgical spleen clinic, however, not a single case was noted (19). Interestingly, studies from the early part of this century reported a much greater incidence of the condition in those undergoing splenectomy: 26% of 360 splenectomies reported before 1900 (11) and 13% of the 355 cases reported between 1900 and 1908 (20) were performed on wandering spleens. One possible reason for the marked difference in incidence over time may be the shift from medical (for example, malaria) to traumatic indications in the majority of splenectomies performed.

A collective review of 97 cases of wandering spleen demonstrated a marked predilection (ratio of 20:1) for women of all age groups (21). However, a separate review of the literature revealed that three times as many males were reported with wandering spleen in 24 patients aged under 10 years (15, 22–30).

Patients with wandering spleen can exhibit clinical findings varying from an asymptomatic abdominal or pelvic mass to an acute surgical abdomen, as illustrated by the case presented. The observed symptoms depend upon the position and pathophysiologic state of the spleen and its pedicle. Most commonly, the enlongated pedicle becomes constricted to varying degrees by rotation of a linear or looped segment of pedicle, yielding torsion or volvulus of the pedicle, respectively. Venous occlusion results in congestion and progressive engorgement of the spleen, stretching its capsule and resulting in pain referred to the epigastrium (1, 4, 5). The nature of the pain is believed to reflect the degree of occlusion of the vessels within the pedicle. Chronic episodic pain or acute severe pain may reflect ability or failure of the pedicle to untwist. Prolonged venous occlusion results in inflammatory perisplenitis, localized peritonitis, splenic adhesions, and eventual thrombosis of the splenic vein. Rarely, acute and complete occlusion of the splenic vessels can result in hemorrhagic infarction with subcapsular hemorrhage, gangrene or splenic atrophy (1, 4, 5, 31). Involvement of the tail of the pancreas (1–5, 21, 32, 33) or greater curvature of the stomach (2, 4) in the splenic pedicle has resulted in necrosis of these structures.

Compression of a hollow viscus between a wandering spleen and the abdominal or pelvic wall can induce symptoms of urinary (2, 4, 34) or gastrointestinal obstruction (1–5, 21).

Formation of bladder adhesions can result in dysuria or incontinence of urine, whereas similar involvement of the uterus may elicit dysmenorrhea or abnormalities of menstrual flow and has also complicated vaginal delivery (4, 12, 35). Translocation to the pelvis may pose a particular diagnostic challenge because of the similar physical findings seen in more common conditions such as ectopic pregnancy, tubo-ovarian abscess, infarcted ovarian tumor, and pedunculated uterine fibroid or ovarian cyst with torsion (2–5, 12, 35).

In pediatric cases, wandering spleen may initially be mistaken for Wilms' tumor. Rare presentations have included displacement into peritoneal sacs of ventral and inguinal hernias (1, 2, 4).

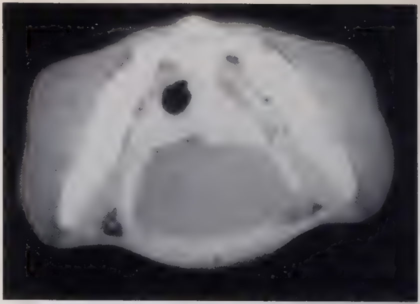

Fig. 2. Computed tomography of pelvis. Pelvic mass reveals several foci of reduced density consistent with hemorrhagic infarction.

Anatomic Considerations. The position of the spleen in the left hypochondrium is normally maintained in two ways: by ligaments which fix and/or support the spleen, and by other contiguous organs and structures which limit its mobility. Although anomalies of contiguous, nonligamentous structures are sufficient to allow the spleen to become abnormally positioned, alterations in the ligamentous elements are necessary to produce wandering spleen. A variety of congenital and acquired factors are believed responsible for the ligamentous changes. In the vast majority of cases, more than one factor is involved; it is therefore useful to consider the etiology of wandering spleen from an anatomic perspective.

Splenomegaly. Progressive splenomegaly may allow for enhanced splenic mobility, if the pressure exerted by an enlarging spleen on surrounding structures (or the weight of the spleen itself) exceed the capacity of the ligamentous attachments to provide adequate fixation and support. Specifically, progressive tension exerted on suspensory ligaments may elicit a breakdown in their elasticity and/or resiliency with a concomittant stretching. Wandering spleens have frequently been reported in cases of splenomegaly, most notably malaria (11, 15, 20, 21, 36, 37) and "big spleen disease" (36); isolated cases have been reported in association with hemorrhagic splenic cysts (4, 5, 21, 31), Hodgkins disease (5, 21), autoimmune hemolytic anemia (38), typhoid fever (20), and idiopathic hypersplenism (38, 39). However, several factors mitigate against splenomegaly as a major etiologic factor. Many asymptomatic wandering spleens are of normal size, or only moderately enlarged (2, 4, 21). When the diagnosis of wandering spleen is made after onset

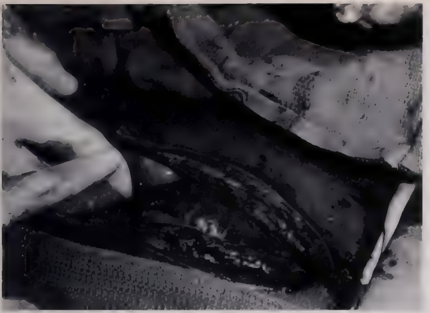

Fig. 3. Dislocated, wandering spleen visualized immediately after abdominal incision. Adhesions were found between spleen and bladder, uterus, and appendix.

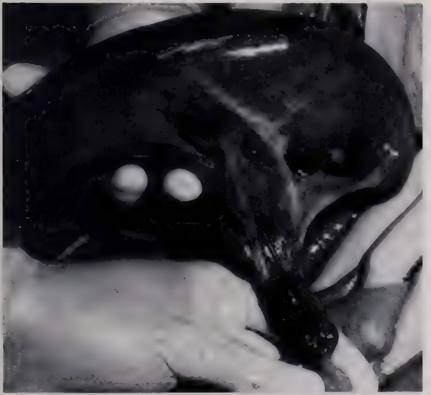

Fig. 4. Enlongated splenic pedicle after mobilization of splenic adhesions and detorsion of pedicle. Stricture of pedicle caused by torsion is seen between surgeon's fingers.

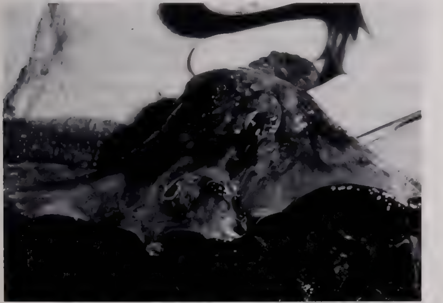

Fig. 5. Partial dissection of spleen revealed thrombi in main splenic vessels, parenchymal congestion, and hemorrhagic infarcts.

of symptoms, splenomegaly is more often secondary to twisting or compression of the pedicle and resultant congestion, rather than a precursor of "wandering." Although malarial hypertrophy has been reported in early studies (9–11) and in current studies from endemic areas (15, 36, 37) as prevalent among those with diagnosed wandering spleen, in many other conditions associated with splenomegaly, no cases of wandering spleen have been noted. However, splenomegaly itself may create a physical impediment to splenic mobility.

Ligaments and Other Contiguous Structures. The spleen develops as a proliferating, mesodermal blastema in the dorsal mesogastrium, ventral to the developing pancreas and dorsal to the stomach. Rotation of the stomach and leftward extension of the omental bursa brings the spleen and the tail of the pancreas to the posterolateral region of the abdominal cavity. A portion of the mesentery dorsal to the spleen, which contains the pancreas, fuses with the peritoneum of the posterior abdominal wall as far as the superior border of the left kidney; the remnant connecting the fused portion with the spleen forms the splenorenal ligament, and carries the splenic vessels. The segment of mesentery ventral to the spleen remains to form the gastrosplenic ligament, and becomes vascularized by the left gastroepiploic and short gastric branches of the splenic artery to supply the greater curvature of the stomach. The phrenicocolic ligament acts as a "sling" to support the inferior pole of the spleen.

These three ligaments comprise the major support and fixation for the spleen. In addition, the phrenicosplenic and splenocolic ligaments stabilize the superior and inferior poles of the spleen, respectively, but are absent far more frequently than the other three ligaments.

Congenital anomalies of the various splenic ligaments have been proposed as etiologic factors for wandering spleen (15, 33, 40). Truesdale and Freedman (40) proposed that inadequate development of the gastrosplenic ligament may be responsible in many cases. The malformation or absence of the gastrosplenic ligament is noted in the vast majority of cases of wandering spleen at the time of splenectomy (2, 4, 21). Several reports, however, have noted enhanced splenic mobility in the presence of a normal gastrosplenic ligament when excessive dilatation of the stomach has developed (4, 38, 41). These cases can be considered wandering spleens because the splenorenal ligament must also be defective, if splenic mobility is markedly enhanced. The frequent absence of the splenorenal ligament has been interpreted by Woodward (33) to signify a failure of the mesogastrium dorsal to the spleen to fuse completely with the posterior abdominal wall. Numerous cases in which the splenorenal ligament is absent and the vascular pedicle of the spleen contains the tail of the pancreas are considered to arise by this mechanism (1–5, 21, 32, 33).

Carswell (15) has attempted to consolidate both theories by proposing that the condition results from a generalized defect in development of the dorsal mesogastrium. He noted that juvenile cases among Africans were frequently accompanied by hypermobility of the cecum, ascending or descending colon due to defects in their respective mesenteries, and suggested a hereditary basis for these defects.

One alternate explanation is that maldevelopment of the phrenicocolic ligament may eliminate a splenic support necessary for normal development of the ligaments derived from the dorsal mesogastrium. That ligamentous anomalies arise congenitally is well-supported by observations of wandering spleen in patients less than two years old (22, 23, 27, 28); the youngest reported was a 17-day-old boy (26). However, it remains unclear to what extent acquired splenomegaly can elicit the same ligamentous changes attributed to a developmental defect.

A more generalized defect in gastrointestinal support is believed responsible for the condition of visceroptosis, a presumed congenital anomaly in several reported cases (4, 5, 42–44). Diminished support of the entire abdominal cavity is deemed responsible for wandering spleen in three infants with "prune belly syndrome" (27, 28). Flaccidity of the abdominal wall has been implicated as a factor predisposing parous women to develop the condition; Abell (21) reported that greater than two-thirds of all women with wandering spleen had given birth at least once. The difficulty with attributing the condition to abdominal flaccidity from multiparity is the same as for malaria: the incidence of wandering spleen among large populations with the risk factor in question is much lower than would be expected if that risk factor were acting independently.

Other conditions reported in association with wandering spleen have included enlargement (45), congenital absence (22, 30), or surgical removal (30) of the left kidney. Because the inferior pole of the spleen rests partly on the left kidney, it is possible that gross abnormalities of renal structure may influence splenic mobility. Finally, marked abnormalities in the configuration of the abdominal cavity have been implicated as possible etiologic factors for wandering spleen in several patients with severe kyphoscoliosis (14, 21, 46).

Diagnosis. A triad of physical findings have been presented by Gindrey and Piquard (37) to suggest a diagnosis of wandering spleen: (a) resonance to percussion in the left upper quadrant, (b) ovoid abdominal mass which is dull to percussion and has a notched border, and (c) movement of the mass toward the left hypochondrium is painless, but motion in any other direction is painful. Obviously, a diagnosis based on physical findings alone becomes difficult when the wandering spleen has become fixed secondarily ("dislocated"). If a true wandering spleen exists, ultrasound and roentgenographic imaging techniques are confirmatory for Gindrey and Piquard's triad; with dislocation of the spleen, imaging (or other) techniques are imperative for accurate diagnosis. Gordon et al. (38) have assembled an array of imaging modality findings which are characteristic for nearly all patients with wandering spleen. These are summarized and critiqued below.

Abdominal x-ray will almost invariably demonstrate loops of bowel in the left upper quadrant; the splenic shadow, if identifiable as such, is abnormally positioned, more radiolucent, and usually larger than normal. The stomach may be dilated and/or abnormally low-lying, and the left kidney may be elevated. The latter can also be demonstrated with intravenous pyelography.

Barium enema revealing marked medial displacement of the splenic flexure is usually indicative of absence of the phrenicocolic ligament; rarely, the spleen or its pedicle may be visualized by compression or stricture of the bowel wall.

Upper gastrointestinal series are informative only when the gastrosplenic ligament is intact or when small-bowel obstruction exists. Although angiography is the only technique which would confirm partial torsion of the splenic pedicle, its expense, risks, and requirements for skilled personnel render it less desirable. Like angiography, spleen or liver-spleen scanning with radioisotopes necessitate adequate splenic perfusion, but offer the advantages of lower cost and reduced radiation dose for the patient (47).

Liver-spleen scanning utilizes ^{99m}Tc-labelled sulfur particles averaging 1 μm diameter, which are taken up by the splenic and hepatic mononuclear phagocytic system (48). Selective splenic scanning may be accomplished by use of erythrocytes from the patient which have been labelled with ^{51}Cr or ^{99m}Tc and heat-damaged (47, 48). Ultrasonography may help in confirming absence of the spleen from its normal position or in confirming identity of the spleen by visualizing the splenic hilum or incisurae lienales (49–51). However, presence of gas-filled, distended loops of bowel in patients with reflex ileus or mechanical obstruction will interfere with ultrasonographic imaging.

Summary

Wandering spleen is a rare yet curious condition which merits attention because of the potential for serious, possibly life-threatening complications. In addition, the clinical manifestations are so variable that diagnosis is commonly missed unless the condition is suspected outright. From available evidence (2, 4, 5) it appears that the majority of diagnoses are made in patients who experience moderate, if any, symptoms. In these patients, findings from roentgenographic, radionuclide, and ultrasound studies are almost invariably diagnostic.

The correct diagnosis of uncomplicated wandering spleen is important both to minimize morbidity and mortality and because diagnostic imaging procedures become problematic once significant complications have developed. The risk for mortality when the condition becomes acutely symptomatic due to torsion of the splenic pedicle has been reported to be as high as 50% (21). The increased risk for rupture of a wandering spleen also poses a significant risk for mortality, although there is insufficient data to accurately assess the level of risk. In spite of potential problems which might be encountered in diagnosing the condition after complications have developed, surgical exploration is diagnostic, and if accompanied by splenectomy, therapeutic.

The optimal management of asymptomatic, uncomplicated cases of wandering spleen has remained controversial. Although splenectomy is most widely accepted as the treatment of choice, both splenopexy and noninvasive management have been successfully employed. The lack of data on the prevalence of wandering spleen and the incidence of complications among asymptomatic cases makes objective evaluation of splenectomy versus other management approaches difficult. In the case presented, however, the failure of expectant management would lend support for splenectomy, splenopexy, or perhaps even autologous, omental implantation of splenic slices as preferable options to management of uncomplicated wandering spleen.

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Polymyositis and Dermatomyositis

Steven R. Ytterberg and Thomas J. Schnitzer

Guest Editors

Veterans Administration Medical Center
Bronx, New York

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The Mount Sinai Journal of Medicine
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Introduction

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Polymyositis and Dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are intriguing inflammatory myopathies which represent challenges for the clinician and the investigator. PM and DM share a number of features, notably proximal muscle weakness clinically and inflammatory myositis histologically. The principal difference between them is the presence of a skin rash in DM; otherwise clinical findings and laboratory features can be identical.

Recent investigation has added significantly to our understanding of pathogenetic mechanisms in PM and DM, although the etiology of each remains unknown. In this issue of *The Mount Sinai Journal of Medicine* we have collected reviews of several important topics pertinent to PM and DM. The clinical overview reviews general clinical features of PM and DM and includes a discussion of the differential diagnosis of the patient with proximal muscle weakness, the most common clinical finding in these disorders. Separate articles address the performance and interpretation of the most important diagnostic tests for the diagnosis of PM and DM, electromyography and muscle biopsy. Further articles discuss childhood disease and its special features, and heart disease in PM and DM. Studies of the epidemiology of PM and DM are providing important information about potential host genetic factors which predispose to disease, as well as potential etiologic agents. Among clinical issues, the relationship of PM and DM to malignancy is one of the most controversial. This topic is reviewed in an article which examines recent case-control studies of PM and DM with malignant disease. The treatment of PM and DM remains largely empirical; current approaches to treatment and experimental modalities currently under investigation are described. Finally, we have included reviews of recent basic investigations which are providing important new insights into understanding the etiology and pathogenesis of these disorders. These articles include discussions of the roles of humoral and cellular immunity in PM and DM, as well as a review of animal models of the disorders which are being studied.

A major problem in understanding PM and DM lies in the fact that the distinction between them has not always been made clear in published reports. This lack of distinction has occurred because of the clinical similarities between PM and DM and the fact that the clinical differences between them and other clinical subgroups of disease have been stressed for less than 15 years. This has led to some confusion in trying to interpret findings of papers. It has also led many authors to use the omnibus term "polymyositis/dermatomyositis" in discussing these disorders, as is evident in the titles and text of the articles presented here. Recent research advances have helped us to understand the distinctions between PM and DM. In truth, however, the etiology and pathogenesis of each are not yet completely understood and, until they are, the designation "PM/DM," although imprecise, will undoubtedly remain in the literature.

Although PM and DM are relatively rare disorders, they are important because of what they can teach about autoimmune disease. We hope that this series of articles summarizing the current state of understanding of these disorders will be of clinical usefulness to physicians who care for patients with PM and DM.

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Overview and Clinical Manifestations of Inflammatory Myositis: Polymyositis And Dermatomyositis

STEVEN L. STRONGWATER, M.D.

Polymyositis (PM) is a progressive inflammatory disease of muscle whose initial symptom is limb-girdle weakness. Inflammatory myopathy associated with skin disease is termed dermatomyositis (DM). Both PM and DM were described in the mid to late 1800s (1–3) and were considered rare until a relationship between malignancy and DM was suggested. This observation focused attention on PM and DM and led to a more comprehensive understanding of the epidemiology and clinical manifestations of these disorders.

A number of syndromes are recognized under the broad heading of polymyositis. Classification schemes based on clinical symptoms or disease associations separate patients into five groups (4):

1. Idiopathic polymyositis
2. Idiopathic dermatomyosis (myositis and characteristic rash)
3. Myositis with features of other connective-tissue disease (overlap group)
4. Idiopathic myositis of childhood
5. Myositis associated with malignancy

A sixth group, consisting of several less commonly encountered forms of myopathy, has been suggested (5–7):

6. Miscellaneous
   Inclusion-body myositis
   Eosinophilic polymyositis
   Localized nodular myositis
   Proliferative myositis
   Infectious myositis

Recent advances in molecular and cellular biology have improved our understanding of the etiology and pathogenesis of PM and DM. By using the Hep 2 substrate, immunoprecipitation or enzyme-linked immunosorbent assays (ELISA), antinuclear antibodies can now be detected in 80% to 90% of patients (8). Circulating antibodies to a host of subcellular particles have been identified which have potentially important clinical and pathophysiologic implications (9); for example, antibody to the Jo-1 antigen identifies a subgroup of patients at risk for interstitial lung disease (10). The Jo-1 antigen is histidyl-transfer RNA synthetase, an enzyme involved in "charging" histidine to its transfer RNA in the process of constructing new proteins (11). This discovery, as well as the detection of antibodies to other charging enzymes, suggests a potential etiologic relationship of PM to viral infection (10, 11). The application of monoclonal antibody technology to histologic muscle specimens has also made it possible to examine the role of the membrane attack complex of complement (12, 13) and cellular elements, like helper and suppressor lymphocytes, killer and natural killer cells, in PM and DM (14, 15).

In addition, newly described animal models are being used to explore the role of the immune system in murine virus-induced myositis (16–18). Of particular interest has been the description of inflammatory myositis in monkeys with acquired immune deficiency syndrome (AIDS) caused by infection with a similar retrovirus (SAIDS) (19). The implication that patients with AIDS could develop PM or DM has now been confirmed (20). Because of the growing number of persons with AIDS, it is possible that many more cases of PM and DM may occur. This further suggests an etiologic association of human disease

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TABLE 1

Drugs Implicated in Human Muscle Disease

Proximal myopathies with elevated muscle enzymes	Possibly assoc. with proximal myopathy	Proximal myopathy due to hypokalemia	Rhabdo-myolosis	Subacute painless proximal myopathy	Focal myopathy*	Myasthenic syndrome	Malignant hyperpyrexia
Clofibrate e-aminocaproic acid Emitine Heroin Alcohol Vincristine Colchicine D-penicillamine	Isoethrine Danazol Cimetidine Metolazone Bumetanide Lithium	Diuretics Purgatives (bulemia) Liquorice Carbenoxolone Amphotericin B	Heroin Amphetamines Phencyclidine Alcohol	Chloroquine Hydroxychloroquine Corticosteroids Alcohol Perhexilene	Meperidine Pentazotacine ?Opiates	Aminoglycosides Polymyxin B Tetracyclines Succinyl choline D-penicillamine Propanolol Practolol ?Other beta blockers Phenytoin Chlorpromazine Procainamide Trimethadion	Suxamethonium Halothane Diethyl ether Cyclopropane Chloroform Methoxyflurane Ketamine Enflurane Psychotropics

* Drugs given intramuscularly.

Adapted from references 23–26.

with either viral infection or aberrations in the immune system.

The introduction of diagnostic assays, techniques to measure muscle strength more accurately, and new imaging studies has improved our understanding of PM and DM. These advances have provided a broad spectrum of research challenges for the coming years.

Clinical Presentation

Polymyositis or DM may occur at any age, but the peak incidence in children is in the group aged 10 to 15 years and, in adults, in the age group 50 to 60 years (21, 22). Onset has been associated with the use of certain drugs (Table 1) (23–26); viral or parasitic infection (27); immunologic disorders, including other connective-tissue diseases (Table 2) (4–7, 21, 28–33); and malignancies (34–37). Although familial cases are rare, genetic susceptibilities (children HLA B8 and Dw3; white adults HLA B8, B14; black adults HLA B7 and DRw6) have been described (22). Further details are presented in the article by Hochberg in this issue.

TABLE 2

Immunologic Disorders Reported in Association with PM and DM

Connective-tissue syndromes	Other immunologic disorders
Eosinophilic fasciitis Psoriasis Rheumatoid arthritis Sarcoidosis Scleroderma Sjogren's syndrome Systemic lupus erythematosus Vasculitis (polyarteritis nodosa)	Agammaglobulinemia Amyloidosis Celiac diseases Complement (C2) deficiency Diffuse interstitial pulmonary fibrosis AIDS IgA deficiency Malignancies Myasthenia gravis

Dermatomyositis is the predominant form of muscle disease in children. Children account for 7% to 20% of polymyositis in large series (Table 3). Both sexes are affected equally under age ten, but in the group aged 10 to 14 years, males develop disease twice as often as females (4–7). Childhood DM begins most frequently in the months of January, February, and March (22). In adults, women develop disease twice as often as men. In the group over age 55, black women have a tenfold increase in disease compared to age-matched controls (38).

Muscular Manifestations

Muscular Symptoms. The clinical hallmark of PM is weakness. It develops acutely or hyperacutely in approximately 3% of patients, subacutely in 67%, and chronically in 30% (21, 32). Weakness has been reported in 89%–100% of patients with PM and DM (Table 4). Prior to the onset of weakness there may be fatigue or modest weight loss (27). In practical terms, weakness can be overwhelming or progress gradually. It usually affects the proximal musculature, muscles of the neck, shoulders, or hip girdle, symmetrically.

Distinguishing the pattern of muscle weakness is important to facilitate diagnosis. Proximal weakness leads to a variety of symptoms depending on the degree and extent of involvement: with shoulder-girdle weakness there may be difficulty performing common tasks, such as combing hair or lifting objects above one's head; hip-girdle weakness may manifest as a clumsy gait or trouble climbing up stairs; neck-muscle weakness leads to trouble raising the head from a pillow.

TABLE 3
Polymyositis: Comparison of Disease Subsets

Series/year pub (ref)	N	PM	DM	Overlap	Malignancy	Childhood %	Type of study	Location
		% (%)*	% (%)*	% (%)*	% (%)*			
Bohan et al 1977 (4)	153	34 (37)	29 (32)	21 (22)	9 (9)	7	Retrospective University	LA, Calif. USA
Henriksson & Sandstedt 1982 (7)	107	44 (54)	15 (19)	15 (19)	6 (8)	20	Retrospective University	Linkoping Sweden
Hoffman et al 1983 (29)	27	41 (41)	22 (22)	30 (30)	7 (7)	0	Retrospective Community	Cooperstown & New York, NY USA
Benbassat et al 1985 (32)	92	20 (25)	31 (40)	13 (17)	14 (18)	22	Retrospective University	Jerusalem & Beer Sheva Israel
Holden et al 1985 (33)	36	50 (50)	14 (14)	25 (25)	11 (11)	NA†	Retrospective University	Calgary Canada
Tymms & Webb 1985 (31)	105	30 (30)	17 (17)	38 (38)	15 (15)	NA	Retrospective University	Sydney Australia
Hochberg et al 1986 (30)	76	41 (41)	27 (27)	24 (24)	8 (8)	Excluded	Retrospective University	Baltimore, Maryland USA

NA, data not available.
* Numbers in parenthesis indicate percent excluding childhood DM.
† Childhood disease not identified as a separate subset.

Myalgia occurs in 25% to 73% of patients (Table 4). Edema of the tissue overlying sore muscles is infrequent and tends to occur in patients with acute or hyperacute presentations (21). Deep tendon reflexes are usually maintained or decreased in proportion to strength. Muscle fatigability, which occurs in myasthenic syndromes, is not a common feature of PM (21). Generally, muscle bulk is normal or slightly reduced until late in the disease, when atrophy and contracture can develop.

Facial weakness is unusual and when it does occur may be difficult to distinguish from forms of muscular dystrophy: in children and adolescents, Landouzy and Dejerine VonGraefe-Fuchs dystrophy; in adults, oculopharyngeal and myotonic dystrophies (39). However, difficulty chewing (40), dysphonia, nasopharyngeal aspiration, and dysphagia, due to pharyngeal muscle weakness, occur in 10% to 35% of patients (39). Other forms of clinically important skeletal muscle involvement include weakness of the diaphragm and intercostal muscles, which may contribute to pulmonary morbidity, including respiratory failure.

Both cardiac and smooth-muscle abnormalities have also been reported (41–46). Each leads to clinically important symptoms. Cardiac involvement is discussed in a separate article in this issue. With respect to smooth muscle, it has been postulated that the entire gastrointestinal tract may be affected. Although proximal esophageal disease has been recognized for a long time, distal involvement has only recently been described (41–44). Formerly, esophageal disease was thought to arise only as a result of skeletal muscle inflammation in the proximal third of the esophagus. However, DeMerieux et al found 14 of

TABLE 4
Clinical Manifestations of Polymyositis (%) in 8 Series

Clinical characteristics	Devere & Bradley (7) N = 118	Bohan et al (8) N = 153	Henriksson & Sandstedt (11) N = 107	Hoffman et al (10) N = 27	Benbassat et al (20) N = 92	Holden et al (19) N = 36	Tymms & Webb (18) N = 105	Hochberg et al (14) N = 76
Mean age	NR	44	44	59	NR	48	50	45
Muscular symptoms								
proximal weakness	92	98	100	93	94	100	89	93
pain	73	25	NR	59	47	NR	67	59
Fever	NR	NR	NR	NR	22	NR	30	NR
Rash	25	41	42	44	58	28	34	36
Raynaud's phenomenon	36	20	NR	22	NR	NR	41	26
Weight loss	NR	NR	NR	NR	NR	NR	42	NR
Cardiac abnormalities	37	50	49	NR	32	NR	30	37
Pulmonary abnormalities								
chest wall weakness	4	NR	NR	0	NR	NR	4	NR
parenchymal disease	NR	NR	NR	NR	13	14	28	37
Arthritis/arthralgia	20	26	NR	41	42	17	68	29
Dysphagia	28	12	39	NR	38	31	30	45

NR, not reported.

TABLE 5
British Medical Research Council: Muscle Strength Determinations

Grade	Strength
5	Normal power
4	Movement against gravity and resistance
3	Movement against gravity only
2	Movement of a joint but not able to overcome gravity
1	Flicker of muscle contraction
0	No contraction

TABLE 6
Cutaneous and Mucous Membrane Findings in Dermatomyositis

Cutaneous		Mucous membrane
Alopecia	Peau d'orange (cutaneous edema)	Leukoplakia
Blepharitis (dilated ocular follicles)	Poikilodermia	Edema
Bullous hemorrhagic eruption	Periorbital edema	Oral ulcers
Erythematous macular eruption in photosensitive distribution (v-shaped rash on neck)	Periungual erythema (nailfold capillary abnormalities)	Tongue swelling
Gottron's papules	Photosensitive rash	
Heliotrope rash	Radial hyperkeratosis	
Hyper- or hypopigmentation (leukodermia)	Striae atrophicans	
Hypertrichosis	Subcutaneous calcinosis	
Lichen planus	Telangiectasia	
Malignant erythema	Vasculitis	

16 patients to have either structural or functional abnormalities of the distal esophagus by cine radiography. These findings occurred in the absence of proximal esophageal motor disease 70% of the time, suggesting an abnormality in the smooth muscle in the lower two thirds of the esophagus (43).

This work has been confirmed by others, including demonstration of reduced amplitude of lower esophageal sphincter contractions (45). Gastric emptying, as assessed by scintigraphic techniques, may also be abnormal. Horowitz and colleagues found that 8 of 13 patients with PM and DM had delayed gastric emptying times (44). In these studies, gastric and esophageal abnormalities tended to correlate with the degree of skeletal muscle weakness. Histologic specimens have rarely revealed inflammatory changes in the smooth muscle, so the cause of these findings is unclear (44).

Assessment of Skeletal Muscle Strength. Accurate evaluation of muscle strength is important for a proper diagnosis and as a guide to therapy. At the bedside, muscle strength is typically graded according to standards established by the British Medical Research Council (MRC) (Table 5) (47). This scale assesses the ability of muscle groups to act against resistance and is extremely useful when severe weakness is present. More often, however, there may be subtle degrees of weakness which are more difficult to quantitate using this scale.

More precise strength measures have been introduced to help plan therapy. These include (a) the time needed to stand ten times from a standard chair ("timed stands" [48]), (b) isokinetic dynamometric assessment of strength (49) and (c) isometric contraction, measured either by strain gauge (50) or a modified sphygmomanometric technique (51). Measurement of quadriceps strength provides the most accurate, clinically useful data (49). The simplest and least expensive bedside tests are the timed stands and isometric contraction using a sphygmomanometer.

It is equally important to determine if a given patient's complaint of "weakness" is the result of muscle disease. For instance, occasionally a patient will describe "weakness" which comes from an articular or periarticular process, such as rheumatoid arthritis or polymyalgia rheumatica, respectively. Cooperation and maximum effort during the examination will be needed to define the origin of these symptoms. Utilizing more objective measures of muscle injury, such as serum muscle enzymes or electromyography (EMG), is also helpful. Rheumatoid arthritis and polymyalgia rheumatica usually induce no objective weakness, and in patients with these conditions the EMG and muscle enzyme results should be normal.

Cutaneous Manifestations: Dermatomyositis

Rash affects about a third of adults and virtually all children with inflammatory myositis (Table 4). A number of mucous membrane and cutaneous abnormalities have been described (Table 6). The most characteristic lesions of DM are the heliotrope rash, Gottron's sign, and an erythematous macular eruption in a photosensitive distribution on the face and neck.

The heliotrope rash affects the upper eyelids, often with accompanying periorbital edema. It causes a violaceous, lilac-colored discoloration of the eyelids, with closely set telangiectatic vessels (52). Frequently, this rash is one of the earliest manifestations of DM and may precede complaints of weakness (53). Telangiectasia also occurs about the upper lips, on the chin, and periorally on the face.

Gottron's lesions are raised, often scaly plaques or papules, which occur over the extensor surface of joints, particularly the knuckles, and less frequently the elbows, knees, ankles, or extremities (Fig. 1). They may be well circumscribed or ill defined and range in color from red to bluish-red. A necrotic hemorrhagic rash over the phalanges of one hand has also been described, as has alabaster-like, hard atrophic patches around large joints (52).

An erythematous, blotchy, maculopapular eruption affecting the cheeks, bridge of the nose, nape of the neck, front and back of the chest, and extensor surface of the extremities may occur in DM. On the neck, it often has a v-like distribution, suggesting a photosensitive eruption, and it may be exacerbated by sunlight. Lesions may progress to areas of atrophy, leukodermia, or hyperpigmentation (21, 52, 53). The extent and intensity of the rash varies considerably; the skin may be shiny, atrophic, edematous, or quite painful, and may even ulcerate.

Periungual erythema, due to abnormalities in the microcirculation of the nailbed, can be a useful diagnostic finding. Using a widefield dissecting microscope or hand-held ophthalmoscope with oil over the nailbed, the normal vasculature appears as a series of fine hairpin loops. In DM and scleroderma these take on a bushy, branching appearance, interspaced with areas of no capillaries (capillary "dropout") (Fig. 2) (54). Digital infarctions, cuticular hypertrophy, or hyperkeratosis may also occur (52–53).

Subcutaneous, dermal, intramuscular, and periarticular calcium deposits can occur, being found most often in children (40%). They occur from six months to twenty years after the onset of myositis and can cause ulceration, secondary infection, and deformity of the overlying skin (53).

Other dermatoses have been described in DM (Table 6). Generally, skin disease either parallels the course of myositis or progresses independently (21). Importantly, cutaneous vasculitis may be a risk factor for concomitant cancer (55) (Fig. 3). Malignancy has been described in 28.6% of patients with vasculitis, compared to 5.8% of patients without vasculitis (55). Despite this, there is no rash that of itself signifies a diagnosis of cancer. Patients with myositis and other connective-tissue disorders (overlap group) have dermatologic abnormalities reflecting their underlying diagnosis, such as proximal scleroderma, acrolysis, sclerodactyly, alopecia. Infectious disorders that may be confused with PM (toxoplasmosis, endocarditis, trichinosis) frequently have dermatologic manifestations which are important diagnostic clues (56).

Extramuscular Manifestations

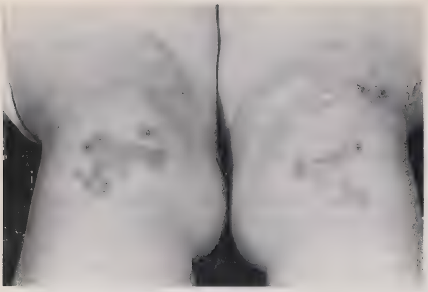
Polymyositis and DM are primarily disorders of skeletal muscle, but it is now clear that visceral organs can also be affected. Disease can involve the pulmonary, cardiac, articular, gastrointestinal, and vascular systems. Organ dysfunction occurs even in patients without "overlap syndromes."

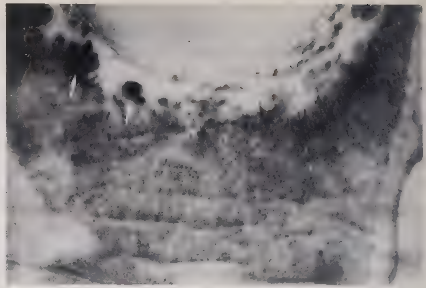
Raynaud's phenomenon occurs in approximately 20% to 41% of patients, most often in patients with overlap syndromes (Table 4). Both cutaneous and systemic vasculitis have been reported, the latter being more common in children (21, 55, 57). Renal failure is a rare complication in PM or DM; it may result from systemic vasculitis or be due to acute tubular necrosis from rhabdomyolysis and myoglobinuria (21, 27).

Arthralgia or arthritis occur in 17% to 68% of patients (Table 4). Arthritis is typically symmetric and nonerosive, affecting the proximal interphalangeal, metacarpalphalangeal, wrist, and knee joints (58, 59). Carpal tunnel syndrome occurs in some patients with wrist involvement (59). In 5 of the 9 patients described by Schumacher et al, arthritis preceded myositis by up to three months. All of these patients had interstitial lung disease, suggesting a pathogenetic association (59). Synovial fluid analysis revealed leukocyte counts ranging from 650 to 5280 cells/ mm^{-3} (650–5280 × 10^6/L), which were predominantly small lymphocytes. Joint subluxation, and periarticular calcifications in association with synovitis, have also been described. The latter form of arthritis is postulated to result from calcium hydroxyapatite deposition (59).

Laboratory Evaluations

Muscle Enzymes. Muscle cell damage results in release of a variety of substances normally contained by vital myocytes into the circulation. These substances, and antibodies made to them, can be measured. Antibodies to subcellular particles are often present and have important diagnostic implications. Commonly, elevations in proteins like myoglobin (elevated in 50% of patients) (22), and enzymes like creatine kinase (CK), aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), mitochondrial aspartate aminotransferase (60), lactate dehydrogenase, and aldolase, which are released from muscle cells, can be detected in serum. These serologic measures fluctuate in parallel with disease activity (4–8, 28–30). Creatine kinase and aldolase are most commonly followed in evaluating muscle injury and in monitoring the effectiveness of therapy.





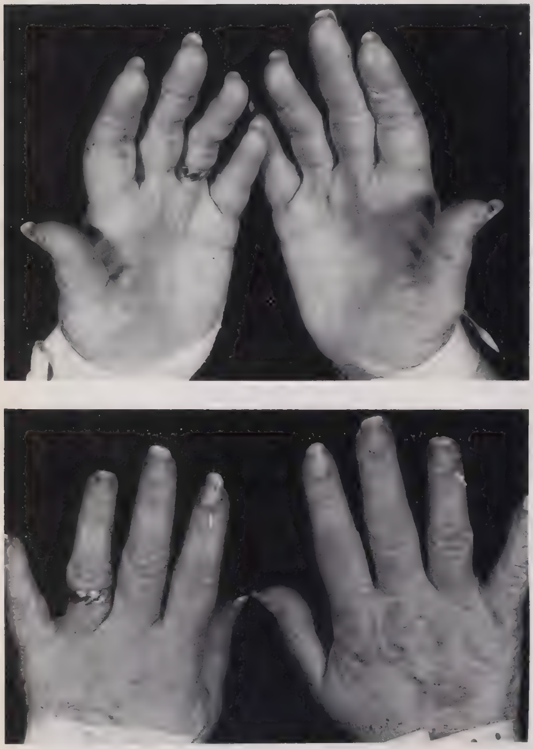


Fig. 1. Above left Gottron's lesions as seen on extensor surface of knees in patient with dermatomyositis.

Fig. 2. Above right Nailfold capillary microscopy in patient with dermatomyositis. Note bushy and dilated appearance of capillaries (arrows). (Original magnification approximately 25 ×)

Fig. 3. Cutaneous infarctions in patient with dermatomyositis and vasculitis. Note lesions at base of nailbed.

Normal values for creatine kinase vary among healthy subjects. Black et al measured CK levels in 307 healthy volunteers and found levels for blacks were higher than those in whites or Hispanics (61). Comparing CK activity to accepted laboratory normals, 65% of black men and 54% of black women had abnormal elevations. Mean levels were 146 ± 137 U/L for men and 66 ± 50 U/L for women; "normal values" in these researchers' laboratory were 8–80 U/L for men and 5–50 U/L for women (61). These data show that it is imperative to consider the patient in question when interpreting laboratory results. Exercise such as jogging, increases in muscle mass (weight lifters), and a variety of toxins and drugs, as well as metabolic and neurologic disorders can affect CK activity (Table 7). Ogasahara et al studied six patients with PM and DM before and after exercise and reported an increase in post exercise CK from 122% to 223% above baseline (60). On the other hand, CK levels may be low in early pregnancy, in connective tissue diseases (systemic lupus erythematosus), or as a result of treatment with drugs including steroids, heparin and phenothiazines (62).

Creatine kinase levels are typically elevated in patients with active myositis. Yet in large series, there are some patients who have normal activity (4–7, 28–30). Fudman and Schnitzer reviewed seven patients who had normal CK levels with definite or probable DM. Five of the seven had either interstitial lung disease or cancer, suggesting that this group has a poorer prognosis (63). The explanation for the disparity between clinically active PM and normal CK levels is unclear. Kagen and Aram described an inhibitor of CK activity in sera from some patients with PM (64). In addition to leading to an underestimate of CK activity, the amount of inhibitor correlated with disease severity, such that the weaker the subject, the greater the degree of CK activity inhibition. This phenomenon also occurred in patients with other myopathies and in patients post-surgery, suggesting the inhibitor was released from injured muscle. Aldolase activity was not affected by the inhibitor. It is of note that Fudman and Schnitzer's patients with normal CK activity had elevations in other muscle enzymes (63), perhaps suggesting a technical problem in assaying CK like Kagen and Aram's inhibitor. This finding provides some explanation for the varied CK activity observed.

Under circumstances in which the CK level is normal and confusion still exists about the presence or absence of muscle disease, quantitation of urinary creatine can be helpful. Creatine is synthesized in the liver, kidney, and probably pancreas, and taken up by muscle cells (65). In the presence of metabolic or inflammatory muscle disease, myocyte uptake of creatine falls and increased amounts are excreted in the urine. Creatinuria may be the most sensitive abnormality in steroid myopathy in which CK activity is usually normal and EMG findings are nonspecific (66). Urinary creatine excretion is routinely high during active PM and DM.

In serum, creatine kinase exists as a family of electrophoretically distinct isozymes: MM, MB, and BB. Each isozyme is predominantly contained in one organ system; injury to skeletal muscle normally leads to the release of CK-MM, cardiac tissue CK-MB and brain CK-BB activity. Moreover, each isozyme can be post-synthetically modified, with the formation of subisoenzymes. As many as twenty one CK-MM subisoenzymes can be detected by isoelectric focusing (67).

CK MB isozyme levels are often elevated in PM and DM (68). Interpretation of this finding is complicated because myocarditis can occur in PM. Indeed, increases in CK MB have been proposed as a marker for myocardial involvement (46). However, skeletal muscle can make the CK MB isozyme. Developing myocytes switch their synthetic pattern from one isozyme to the next, initially making BB, then MB, and finally MM. Regenerating muscle cells in PM are likely doing the same (69). Along these lines, it is of note that male marathon runners also have increases in MB activity in the absence of cardiac disease (70). Whatever the correct interpretation for elevated levels, it is important to recognize that up to 10% CK MB in patients with myositis does not necessarily imply myocardial disease.

Analysis of CK MM subisoenzymes provides insight about the course of skeletal muscle inflammation in PM at a given point in time (71). Normally, CK MM subisoenzyme 1 is released from damaged muscle and is successively converted to a number of other subisoenzymes. Annesley et al, employing an agarose gel electrophoretic technique capable of detecting three subisoenzymes, MM 1, MM 2 and MM 3, reported an association of worsening disease in PM patients with levels of CK MM 1 less than 30% of total CK MM, or ratios of MM 3 to MM 1 greater than one (71). This contrasted to MM 1 levels above 30% or MM 3 to MM 1 ratios less than one, in patients who had improving or stable myositis. The changing subisoenzyme pattern results from progressive postsynthetic modification of CK MM by a CK converting factor (CKCF) released from myocytes. During periods of active disease increasing amounts of CKCF are released, thereby driving the conversion of MM 1 to MM 2 and finally MM 3. Comparisons of MM 1 to MM 3, therefore, may provide an index of muscle inflammation (71).

Other Measurements. Fifty percent of patients have an elevated erythrocyte sedimentation rate, exceeding 50 mm/hr in 20% (27). Abnormalities in leukocyte count, hemoglobin, gamma globulins, paraproteins, and immune complexes also occur (27). These findings are nonspecific and of little diagnostic value.

Electromyography and Muscle Biopsy. Electromyography (EMG) is used to distinguish primary inflammatory muscle disease from motor neuron, axonal, neurolemmal, or receptor dis-

TABLE 7

Causes of Elevations in Creatine Kinase

Cardiac	Skeletal muscle	Metabolic/drug*	Central nervous system	Miscellaneous
Catheterization	Dermato/polymyositis	Alcoholism	Acute brain injury	Blood donation
Cardioversion	Intramuscular injections	Clofibrate	Cerebrovascular accidents	Exercise
Myocarditis	Muscular dystrophy	Colchicine	Psychosis	Large muscle mass
Pulmonary edema	Myasthenia gravis	Delerium tremens	Schizophrenia	Noncardiac surgery
Tachycardia	Myopathies	Diabetes mellitus	Seizures	Pancreatitis
	Radiation therapy	Malignant hyperthermia		Pneumonia
	Rhabdomyolysis	Hypokalemia		Pulmonary embolism
		Hypothermia		Reye's syndrome
		Hypothyroidism		Shock
		Ketamine		Trauma
		Retinoids		
		Vitamin C deficiency		

Adapted from Black HR, Quallich H, Gareleck CB. Racial differences in serum creatine kinase levels. Am J Med 1986; 81:479–487.

* See Table 1.

orders (72, 73). It should be performed in all patients with suspected myositis and if done quantitatively, can be used to monitor disease activity (74). The findings in PM and DM include a triad of (a) small amplitude, short duration, polyphasic motor units, (b) fibrillations, positive sharp waves, increased insertional irritability and (c) spontaneous, bizarre, high frequency discharges. In general, clinically weak muscles are abnormal. Henriksson and Sandstedt reported findings in more than 90% of their patients (74). Nerve conduction studies and tests of distal latency are normal, unless severe muscle atrophy precludes an evoked response (22). The disappearance or reappearance of fibrillations suggests a remission or reexacerbation of the myositis, respectively.

Electrical studies are often done unilaterally to avoid traumatizing a muscle intended for biopsy as the needle exam may induce artifacts difficult to distinguish histologically from PM. Muscle which is clinically weak but not atrophic,

TABLE 8

Differential Diagnosis of PM/DM

Neurologic disorders
Acute intermittent porphyria
Autoimmune polyneuropathy
Carcinomatous neuromyopathy
Congenital myopathy
  Nemaline
  Mitochondrial
  Centronuclear
  Central core
Denervating disease
  Spinal muscular atrophy
  Amyotrophic lateral sclerosis
Diabetic amyotrophy, polyradiculopathy
Guillain Barre syndrome
Inclusion body myositis (see Table 9)
Junction disease
  Eaton Lambert syndrome
  Myasthenia gravis
Microembolization by atheroma or carcinoma
Muscular dystrophy
  Duchenne
  Fascioscapulohumeral
  Limb girdle
  Becker
  Emery-Dreyfuss
  Distal
  Ocular
Storage disease
  McArdle's disease
  Acid maltase
  Carnitine palmityltransferase deficiency
  Myoadenylate deaminase deficiency

Endocrine disorders
Diabetes mellitus
Hypo- or hyper-thyroidism
Hypo- or hyper-cortisolism
Hypo- or hyper-parathyroidism
Vitamin D deficiency myopathy

Toxin-induced weakness (see Table 1)
Alcohol
Drugs
  D-penicillamine
  chloroquine
  clofibrate
  emetine
  corticosteroids
  colchicine

Metabolic disorders
Cachexia
Carcinoid myopathy
Diabetes mellitus
Familial periodic paralysis
Hypokalemia, hypocalcemia, hypophosphatasia
Rhabdomyolysis
Uremia, hepatic failure

Infections
Bacterial
  Systemic
    Bacterial endocarditis
  Local
    Staphlococcal (tropical pyomyositis)
    Streptococcal
    Clostridial
    Leprosy
Mycobacterial
Parasitic
  Toxoplasma
  Trichinella
  Schistosomiasis
  Cysticerci
  Sarcosporidia
  Trypanosoma
Rickettsial
Viral
  Influenza
  Epstein Barr virus
    Mononucleosis
    Chronic fatigue syndrome
  Coxsackievirus
  Rubella

Collagen vascular disorders
Fibromyalgia
Giant-cell myositis with thymoma
Polyarteritis nodosa
Polymyalgia rheumatica
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Systemic lupus erythematosus
Wegener's granulomatosus

usually reveals the most useful information. A nondiagnostic exam should be repeated in two to four weeks as an increase in the tempo of disease, as reflected by the appearance of fibrillations, is suggestive of PM. Repetitive stimulation is also helpful to exclude disorders effecting the neuromuscular junction.

A diagnosis of PM can only be confirmed by muscle biopsy. The site of biopsy should be carefully chosen as myositis is frequently focal. The results of EMG examination can be helpful in choosing a biopsy site (72), as can quantitative nuclear medicine scans employing gallium citrate and technetium diphosphonate (75, 76). Magnetic resonance imaging has recently been suggested as a useful adjunct for diagnosis and perhaps long term followup, though its widespread utility remains to be determined (77). Atrophic, severely weak muscles should not be biopsied since they are often replaced by fat or fibrous tissue and provide little diagnostic information. Tissue may be obtained by open biopsy or percutaneous needle biopsy (78). Between 10% and 17% of patients will have a normal open biopsy (27). By obtaining two or more surgical specimen, the likelihood of positive findings is increased. Muscles typically biopsied are the deltoid, triceps, biceps and quadriceps. Biopsies should be performed by a skilled surgeon and processed by an experienced neuropathologist to avoid misdiagnosis.

Diagnosis

The diagnosis of PM or DM requires a history consistent with, a physical examination suggestive of, and laboratory findings characteristic of these disorders, including:

1. Symmetrical proximal muscle weakness
2. Elevated serum muscle enzymes (CK, aldolase)
3. Typical triad of EMG abnormalities
4. Typical histology of PM on muscle biopsy
5. Characteristic rash

Patients are regarded as having definite disease in the presence of four, probable disease in the presence of three, and possible disease in the presence of two of these characteristics (see Table 1 in article on epidemiology in this issue) (4).

Differential Diagnosis. Weakness is caused by several pathophysiologic mechanisms. It develops, as in PM, as a result of inflammatory muscle disease, but it can occur in the setting of electrolyte, endocrine, or neurologic disorders, in malignancies (paraneoplastic syndromes—Eaton Lambert syndrome or metastatic carcinomatosis), as a result of toxin exposure, infections, inanition, or inborn errors of metabolism (Table 8).

This long list of disorders makes the differential diagnosis of weakness a challenge. Historical information, clinical findings, and laboratory results provide the clues needed to undertake an appropriate evaluation and reach a correct diagnosis. For example, although PM and DM occur in all age groups, early onset and a history of weakness in close relatives emphasize the possibility of muscular dystrophy, enzyme deficiency state, or storage disease. Ischemic muscle exercise testing, which assesses the ability of muscle to metabolize stored sugars and produce lactate or ammonia, is helpful in identifying the latter.

Some disorders are particularly difficult to distinguish from PM because they are regularly associated with elevated muscle enzymes. These include hypothyroid myopathy (79) and inclusion-body myositis (80, 81). Rhabdomyolysis due to hypophosphatasia, hypokalemia or other toxins, acute myositis following viral infections (postinfluenza myositis), pyomyositis, trauma (including intramuscular injections), and denervating conditions such as amyotrophic lateral sclerosis may also cause increases in CK (Table 7).

Myasthenia Gravis and Eaton Lambert Syndrome. Patients with myasthenia gravis or Eaton Lambert syndrome can be identified by EMG (72–73). Rapid repetitive stimulation performed during EMG produces an increase in action potential amplitude in Eaton Lambert syndrome, in contrast to the reduction in myasthenia gravis. Further, the response to edrophonium or neostigmine characteristically results in improved strength in myasthenia gravis and has a variable effect in Eaton Lambert syndrome. Symptomatically, bulbar or ocular complaints are more common in these disorders than in PM or DM.

Steroid-Induced Myopathy. Steroid myopathy develops in patients requiring extended treatment with high doses of corticosteroids (66). Weakness begins insidiously, usually affecting the proximal musculature of the lower extremities first, and may be accompanied by myalgia. Steroid myopathy may occur in anyone receiving corticosteroids regardless of age or underlying condition. Askari points out that accelerated osteoporosis, as reflected by vertebral fractures, may identify a patient population at increased risk (65). In contrast to PM, patients with steroid myopathy usually have normal serum muscle enzymes. The EMG may reveal a myopathic pattern of small and abundant action potentials, but the fibrillations seen in PM are absent (72, 73).

TABLE 9

Proposed Criteria for Diagnosis of Inclusion Body Myositis

I. Clinical Criteria
A. Proximal muscle weakness (insidious onset)
B. Distal muscle weakness (inability to make clenched fist)
C. Electromyographic evidence of generalized myopathy (inflammatory myopathy)
D. Elevation of muscle enzyme levels (creatine kinase and/or aldolase)
E. Failure of muscle weakness to improve on high-dose corticosteroid regimen (at least 40–60mg/d for 3–4 mo)

II. Pathologic Criteria
A. Electron microscopy (EM) of muscle: inclusions in which microtubular filaments can be identified
B. Light microscopy
  1. Intranuclear and/or intracytoplasmic inclusions
  2. Lined vacuoles

III. Classification
A. **Definite IBM:** presence of clinical criterion IA plus one other clinical criterion and pathology revealing EM abnormality IIA
B. **Probable IBM:** presence of clinical criterion IA plus three other clinical criteria, evidence of intranuclear and/or intracytoplasmic inclusions (IIB) and light microscopy revealing lined vacuoles (IIB)
C. **Possible IBM:** presence of any three clinical criteria with light microscopy (IIB)

Adapted from Calabrese LH, Mitsumoto H, Chou SM. Inclusion body myositis presenting as treatment resistant polymyositis. Arthritis Rheum 1987; 30:397–403.

Patients with PM can also develop steroid myopathy. The clinical picture may be very confusing because both conditions cause weakness and EMG abnormalities. To distinguish between worsening myositis and weakness resulting from corticosteroid therapy, the dosage of corticosteroid can be changed empirically and the patient monitored, or EMGs can be repeated. Alternatively, serial measurements of urinary creatine can be monitored (see Laboratory Evaluations above). In PM and DM, urinary creatine falls in response to therapy, whereas in steroid-induced myopathy creatinuria rises abruptly (66).

Inclusion-Body Myositis. Inclusion-body myositis (IBM), first described in 1967, is a disorder with clinical, electrophysiologic, serologic, and histopathologic findings similar to PM. Most patients with IBM typically fulfill Bohan and Peters' criteria for PM (4). They have progressive proximal muscle weakness, elevations of muscle enzymes, the triad of EMG findings noted in PM, and evidence of inflammatory myositis histologically. It is extremely important to distinguish IBM from PM, because IBM does not respond well to corticosteroids. Calabrese and colleagues speculate that many patients with treatment-resistant PM actually suffer from IBM (80).

IBM has a bimodal age distribution with onset in the second and sixth decade. Clinically, the inability to make a clenched fist, due to more severe distal muscle involvement in IBM, may help differentiate these two disorders. In IBM, muscle enzymes are usually only modestly elevated, ranging from two to seven times normal for CK, whereas in PM enzyme levels may be much higher (80, 81). There is no apparent association of IBM with malignancy, but an association has been reported with chronic immune thrombocytopenia (82), Sjogren's syndrome (83), and systemic lupus erythematosus (84). Positive antinuclear antibody studies have been noted in these patients (82–84).

The main distinction from PM is made histologically, by electron microscopic demonstration of nuclear and sarcoplasmic inclusions with microtubular structures. Subtle differences, including intranuclear or intracytoplasmic inclusions and "lined vacuoles," may also be found under the light microscope. Suggested criteria for IBM include both pathologic and clinical features (Table 9).

Summary

An exhaustive discussion of all the disorders listed in Table 8 is beyond the scope of this overview. However, it is well to keep in mind that many disorders cause weakness. A thorough evaluation therefore includes a careful history and physical examination, measurement of thyroid functions, serum electrolytes, creatinine, calcium, phosphate, magnesium, alkaline phosphatase, total protein and albumin, an evaluation for collagen vascular disease (for example, rheumatoid factor, antinuclear antibody), and if weakness remains unexplained, EMG, ischemic muscle exercise testing and/or muscle biopsy. Additional studies should be performed as warranted clinically or historically (serum cortisol, antibody testing for HIV, roentgen evaluation for cancer, and so on).

Polymyositis and dermatomyositis are disorders that primarily affect skeletal muscle. Exciting clinical and research advances have occurred during the past decade. There is increasing recognition that PM and DM are systemic disorders with clinically important visceral organ involvement. Diagnosis requires a keen understanding of the many causes of weakness and the judicious use of available diagnostic studies.

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Epidemiology of Polymyositis/Dermatomyositis

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Polymyositis is an acquired, inflammatory myopathy of unknown etiology involving striated skeletal and, less commonly, cardiac muscle. Associated clinical features include skin rash (dermatomyositis), dysphagia, arthritis, Raynaud's phenomenon, interstitial lung disease, and other visceral manifestations; however, proximal limb girdle muscle weakness is the dominant feature of this disorder (1). The descriptive, epidemiologic, and diagnostic-classification criteria of polymyositis were briefly reviewed in 1980 at the Fourth International Conference on Epidemiology of Rheumatic Diseases (2); since then, additional data have been published concerning mortality, the role of genetic and environmental factors in etiology, and the course and prognosis of patients with myositis. This article will review these findings and suggest avenues for further research.

Diagnostic and Classification Criteria

The problems inherent in the diagnosis of polymyositis/dermatomyositis were reviewed in 1975 by Bohan and Peter (3). They proposed five major criteria to define polymyositis and dermatomyositis primarily for purposes of clinical research (Table 1). These authors qualified the criteria by stating that "the diagnosis of polymyositis or dermatomyositis is not necessarily excluded by failure to meet them." Furthermore, they enumerated several exclusion criteria, including congenital muscular dystrophies, central or peripheral neurologic disease, infectious myositis, metabolic/endocrine myopathies, drug-induced myopathies, and myasthenia gravis.

Several authors have estimated the sensitivity of these criteria in patient cohorts with polymyositis/dermatomyositis (Table 2) (2, 4–9); the specificity of the criteria when validated against a combined control group of 172 patients with systemic lupus erythematosus and 264 patients with systemic sclerosis was 93% (2).

The generally accepted classification schema for polymyositis/dermatomyositis is that proposed by Pearson (Table 3) (10); the adult disease is separated from the childhood form and, among adults, polymyositis is separated from dermatomyositis. In addition, two clinical subtypes are recognized: the occurrence of myositis either in the setting of malignancy (11) or with an associated connective tissue disease.

Morbidity and Mortality

Morbidity. Polymyositis/dermatomyositis occurs worldwide. Medsger, Dawson, and Masi reported the descriptive epidemiology of polymyositis based on 124 cases admitted to Memphis and Shelby County, Tennessee, hospitals between 1947 and 1968 (12). The overall, average annual age-adjusted incidence rate of polymyositis was estimated as 5.0 cases per million population per year; the average annual incidence rate for the latest five-year period of the study, 1963 to 1968, was 8.4 new cases per million per year for all race-sex groups combined (Table 4). These authors noted a fourfold greater incidence rate among black than among white females over the entire study period.

Additional findings included a bimodal pattern of age-specific incidence rates, with peaks of 3.7 and 4.3 cases per million per year in age groups 5 to 9 and 10 to 14, and 10.1 and 10.3 cases per million per year in age groups 45 to 54 and 55 to 64 years. No significant associations be-

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TABLE 1

Diagnostic Criteria for Polymyositis and Dermatomyositis

Criterion no.	Description
1.	Symmetrical weakness of limb-girdle muscles and anterior neck flexors
2.	Muscle biopsy evidence of myositis
3.	Elevation in serum of skeletal muscle enzymes, particularly creatine kinase
4.	Typical electromyographic features of myositis
5.	Typical rash of dermatomyositis, including heliotrope lids and Gottron's papules

Polymyositis:	Definite	all of items 1 through 4
	Probable	3 of items 1 through 4
	Possible	2 of items 1 through 4
Dermatomyositis:	Definite	Item 5 plus 3 of items 1–4
	Probable	Item 5 plus 2 of items 1–4
	Possible	Item 5 plus 1 of items 1–4

Adapted from reference 3.

TABLE 2

Sensitivity of Diagnostic Criteria for Polymyositis and Dermatomyositis (P/D)

Author (ref. no.)	No. patients	P/D Definite		Probable	
Medsger (2)	120	88	(73%)	23	(20%)
Hochberg et al (4)	76	56	(74%)	20	(26%)
Bohan et al (5)	153	140	(92%)	11	(7%)
Benbassat et al (6)	92	46	(50%)	26	(29%)
Henriksson & Sandstedt (7)	107	87	(81%)	15	(14%)
Hoffman et al (8)	27	17	(63%)	6	(22%)
Tymms & Webb (9)	105	47	(45%)	30	(29%)
Total	680	481	(71%)	131	(20%)

Sensitivity = Number of patients who fulfill criteria ÷ total number of patients with disease in study.

tween polymyositis and any socioeconomic factor were identified. The authors did note a seasonal clustering of onset of childhood cases in February, March, and April in comparison with a random occurrence in adults.

Benbassat and colleagues reported an estimated age-adjusted average annual incidence of 2.2 cases per million, based on 92 cases discharged from hospitals in Israel between 1960 and 1976 (13).

Kurland and colleagues reported an average annual incidence rate of 6 per million, based on 4 cases diagnosed between 1951 and 1967, and an estimated prevalence of polymyositis of 6.3 cases per 100,000 population, based on 3 cases alive and resident in Olmsted County, Minnesota, in January 1968 (14); the prevalence of polymyositis in Kumamoto, Japan was noted to be 5.0 cases per 100,000 (15).

Mortality. Hochberg and colleagues studied national U.S. mortality data for polymyositis/dermatomyositis between 1968 and 1978 (16). A total of 1,986 deaths were attributed to polymyositis/dermatomyositis over that 11-year period: 1,004 in white females, 563 in white males, 291 in nonwhite females, and 168 in nonwhite males. The pattern in age-adjusted average annual mortality rates per million person-years by sex–race group is identical to the pattern in incidence rates (Table 4). Furthermore, there was evidence of synergistic interaction between sex and race in producing the highest mortality rates in nonwhite females as assessed by Rothman's synergy index.

In contrast to the pattern observed in age-specific incidence rates, age-specific average annual mortality rates showed a unimodal distribution, with maximum rates in the group aged 45-to-64 years for nonwhite females, 55-to-64 year age group for nonwhite males, 65 to 74 year age group for white females, and 75 and above age group for white males (Fig.).

Analysis of secular trends in annual age-adjusted mortality rates from 1968 through 1978 revealed significant increases among both white males and white females, which was attributed by the authors to increased physician awareness and diagnosis of these conditions and/or a "true" increase in incidence of polymyositis. Finally, analysis of secular trends in mean age at death from 1968 through 1978 revealed significant increases in age at death among all sex-race groups, which was felt to be most consistent with an improvement in prognosis over time and a concomitant decrease in mortality rates in childhood-onset and young-adult cases rather than an increase in age at diagnosis of polymyositis.

Etiologic Factors

Genetic. Polymyositis/dermatomyositis does not appear to demonstrate familial aggregation, which is seen in systemic lupus erythematosus and rheumatoid arthritis. Familial occurrence has only rarely been reported (17, 18). Hirsch and colleagues studied 53 patients with myositis; all were typed for HLA-A, B, C, and DR antigens, and the results were compared to local controls (19). HLA-B8 was found in 7 (54%) of 13 white patients with polymyositis compared to 19% of over 1,400 controls ($P = .005$), whereas HLA-DR3 was found in 8 (75%) of 12 whites with polymyositis compared to 23% of over 100 controls ($P = .003$). HLA-B7 was found in 6 (67%) and HLA-DRW6 in 7 (78%) of 9 black patients with polymyositis, compared to 26% of 89 and 46 controls, respectively ($P = .02$ and $P = .005$, respectively). No HLA specificities were increased in frequency in the 7 white and 9 black patients with dermatomyositis.

Friedman and colleagues reported results of HLA-A and B locus typing in 67 white patients with juvenile dermatomyositis (20), of whom 36 were also typed for HLA-DR antigens (21). HLA-B8 was found in 37 percent of patients, compared to 17.5% of controls ($P < .01$), whereas DR3 was found in 53% of patients compared to 22.7% of controls ($P < .01$). The association of DR3 but not B8 with juvenile dermatomyositis was also found in Latin American and black patients studied by these authors.

Arnett and colleagues noted an association between the presence of HLA-DR3 and anti-Jo-1 antibody; 7 of 11 patients with anti-Jo-1 antibody were positive for DR3 compared to 8 of 36 patients without anti-Jo-1 antibody (22). Pachman and colleagues, however, were unable to identify any associations between DR3 and clinical or laboratory features in white patients with juvenile dermatomyositis (23).

Infectious Agents. Kagen and colleagues, in 1974, first presented evidence of an association between toxoplasmosis and adult-onset polymyositis (24). They found titers of 1:1024 or above in the Sabin-Feldman dye test in 6 of 10 adult patients with polymyositis compared to 2 of 7 adults with dermatomyositis and only 1 of 35 adult hospital controls. Positive complement fixation antibody tests were found in five, one and one patient in each of these three groups, respectively. Among the polymyositis patients, positive serologic findings correlated with disease duration of one year or less and no prior or concurrent steroid therapy. The authors interpreted their results as consistent with either recently acquired or activated *Toxoplasma* infection in patients with recent-onset polymyositis.

Subsequently, Phillips and co-workers studied 20 patients with polymyositis, 25 with dermatomyositis, and 25 with myositis associated with another connective tissue disease and 69 controls matched on age, sex, race, and hospital (25). Complement-fixing antibodies to *T. gondii* were found in 7 (35%) of polymyositis patients compared to none of 20 matched controls and only 2 of the total 69 controls. No differences were noted in frequency of positive Sabin-Feldman dye tests or any antiviral antibodies; however, myositis patients had higher antibody titers against Epstein-Barr virus than controls. These authors interpreted their results as supporting the findings of Kagen and colleagues (24) and consistent with a role for *Toxoplasma* infection, either primary or reactivated, in the pathogenesis of polymyositis.

More recently, Magid and Kagen found positive Sabin-Feldman dye tests in 19 (76%) of 25 patients with polymyositis compared to 10 (30%) of 33 patients with dermatomyositis ($P = .001$) (26). IgM anti-*Toxoplasma* antibodies, indicative of recent infection, were detected in seven patients in each of the two myositis groups for a total of 24 percent of those studied. The authors felt their data supported the hypothesis that *T. gondii* may be etiologically related to polymyositis.

In addition to *Toxoplasma* infection, antecedent viral infection has also been hypothesized as etiologically related to polymyositis. These investigations were further stimulated by the demonstration that coxsackievirus B1 Tucson strain produced a polymyositis-like illness in infected CD1 Swiss mice (27). Christensen and colleagues performed a case-control study measuring complement-fixing and neutralizing antibodies to coxsackievirus types B1–B6 in 12 children with juvenile dermatomyositis, 24 children with juvenile rheumatoid arthritis matched on age, sex and date of rheumatology clinic visit, and 2192 hospitalized controls with suspected viral infections (28). Ten (83%) of the children with juvenile dermatomyositis had significant levels of IgG complement-fixing antibody to at least one coxsackievirus B antigen compared to 4 (17%) of the arthritic controls and less than 25 percent of the hospital controls. Neutralizing antibodies were also more common in dermatomyositis than arthritis clinic patients. No differences were found

TABLE 3

Classification Schema for Polymyositis and Dermatomyositis

Type	Category
I.	Typical polymyositis
II.	Typical dermatomyositis
III.	Typical dermatomyositis or polymyositis associated with malignancy
IV.	Childhood dermatomyositis
V.	Polymyositis associated with another connective tissue disease (most often Sjogren's syndrome, systemic sclerosis, or systemic lupus erythematosus)

Adapted from Pearson CM. Patterns of polymyositis and their responses to treatment. Ann Intern Med 1963; 59:827–838.

TABLE 4

Morbidity and Mortality Rates for Polymyositis/Dermatomyositis in the United States by Sex-Race Group

	Incidence*	Mortality†
White males	3.7	0.6
White females	6.0	0.9
Black males	10.1	1.2
Black females	18.3	2.2

* Age-adjusted average annual incidence rates per million in Shelby County, Tennessee, 1963–1968 (reference 2).

† Age-adjusted average annual mortality rates per million person-years, 1968–1978 (reference 16).

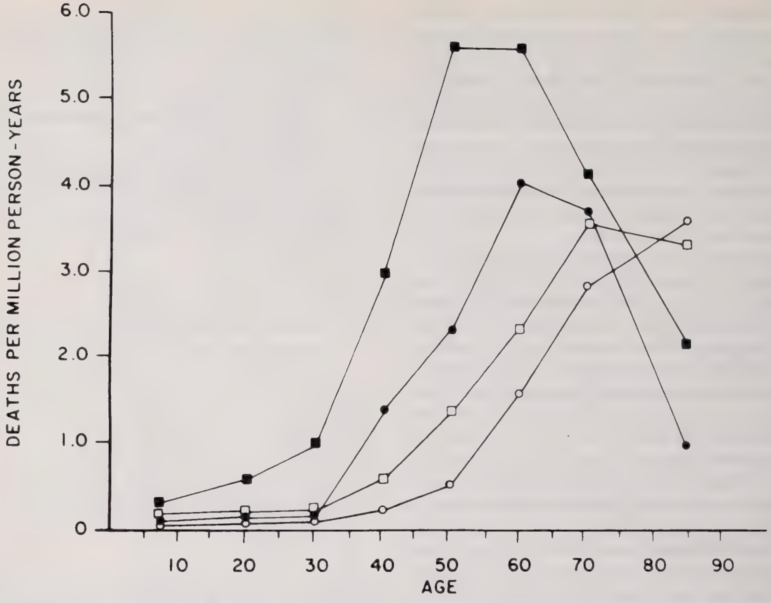

Fig. Age-specific average annual mortality rates from polymyositis/dermatomyositis by sex-race group; ○ = white males, □ = white females, ● = nonwhite males, and ■ = nonwhite females. *Reprinted from a figure in ref. 16, ARTHRITIS AND RHEUMATISM Journal, copyright 1983. Used by permission of the American Rheumatism Association.*

in results of tests for antibodies to 13 other viral antigens and *Mycoplasma pneumoniae* between these two groups. Thus, these data support a role for coxsackievirus B infection as an etiologic factor in juvenile dermatomyositis. Obviously, studies with larger numbers of patients are needed to confirm these findings.

The observations of Walker and Jeffrey also have profound implications concerning the molecular basis of the viral etiology of polymyositis (29). They demonstrated sequence homologies between histidyl-tRNA synthetase, the autoantigen against which the Jo-1 antibody is directed, the light chain of myosin and a hypothetical EC-RF4 protein of Epstein-Barr virus, as well as between alanyl-tRNA synthetase, tropomyosin and four different viral proteins including two from influenza species and one each from Epstein-Barr virus and adenovirus. These homologies support the hypothesis of molecular mimicry—that antibodies initially directed against foreign viral antigens may cross-react with muscle protein and produce myositis.

Finally, of current interest, is the recent report of two homosexual male patients with polymyositis who developed typical acquired immune deficiency syndrome with opportunistic infections within 2 months of beginning high-dose prednisone therapy; immunocytochemical staining of muscle biopsy specimens revealed HIV antigen in inflammatory cells surrounding and invading the muscle fibers (30). Whether the HIV retrovirus was directly involved in the pathogenesis of polymyositis in these two patients is unknown.

Prognostic Factors

Hochberg and colleagues recently reported on the survivorship and prognostic factors in 76 adult patients with polymyositis/dermatomyositis hospitalized from 1970 through 1981 (4). Cumulative survival rates, using life-table methods, were 80.4% and 72.8% five and eight years after diagnosis, respectively. These rates were higher than those of 65% and 53%, five and seven years after diagnosis, respectively, reported in 124 patients discharged from Memphis and Shelby

County, Tennessee, hospitals from 1947 through 1968 (31).

Factors associated with poor prognosis and decreased survival rates include older age at diagnosis (4, 6, 31), cardiac involvement (4, 7), dysphagia (6, 31), and lack of response to corticosteroid treatment (6, 7). The relationship of associated malignancy with prognosis is controversial, some studies supporting a poor prognosis for these patients (5–7) and others finding no differences in prognosis for myositis patients with or without tumor (4, 31).

A generally favorable outcome in long-term survivors was reported by Henricksson and Sandstedt, who noted that 87% of patients who improved with therapy had either slight or no physical disability at followup, in contrast to only 9% of patients who were treatment failures (7). The major factors associated with treatment failure and long-term moderate or severe physical disability was a delay of two years or more from onset of myositis to beginning of steroid therapy. Similar conclusions have been drawn from several series of patients with juvenile dermatomyositis, where a poor long-term outcome is characterized by the development of muscle contractures and calcinosis (22, 32–34).

Summary

Polymyositis/dermatomyositis is an uncommon condition that demonstrates heterogeneity in relation to a bimodal distribution of age at onset, association of antibodies to *Toxoplasma gondii* with adult polymyositis but not dermatomyositis, and an association of Coxsackievirus infection with juvenile dermatomyositis. A genetic predisposition marked by HLA-DR3 is found in several disease subtypes, and prognosis appears to be similar in adult polymyositis and dermatomyositis, suggesting homogeneity in clinical course.

Further epidemiologic studies should include multicenter case-control studies designed to investigate etiologic factors, and controlled clinical trials to evaluate new therapies with outcome measured as muscle strength, performance, and physical disability.

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Pathology of Polymyositis/Dermatomyositis

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This article summarizes pathologic changes in muscle biopsies from adult polymyositis and childhood and adult dermatomyositis, with a brief discussion of inclusion body myositis. More detailed information can be found in several recent publications (1–4).

Methods

Thorough examination of muscle biopsy samples requires a combined approach, utilizing fixed tissue, fresh frozen material, and glutaraldehyde-fixed plastic-embedded material. Inflammatory infiltrates, necrosis, and phagocytosis are all demonstrated well with formalin-fixed, paraffin-embedded material. Cryostat sections, oriented in cross section, of frozen material provide a variety of staining procedures and histochemical reactions, which better evaluate metabolic, structural, and morphometric changes within the muscle. The use of ultrastructural techniques is necessary to demonstrate typical inclusions of inclusion body-myositis. In our laboratory, cryostat sections provide the majority of histologic and histochemical information needed for diagnostic purposes; ultrastructural studies are done as needed.

Polymyositis

Muscle fiber necrosis, often with phagocytosis; endomysial inflammatory infiltrates; and perivascular inflammatory infiltrates comprise the characteristic pathologic triad in polymyositis (1, 4, 5). In a quantitative pathologic study of inflammatory myopathies, Ringel et al found muscle necrosis and endomysial inflammatory infiltrates in nearly 100% of biopsies; perivascular infiltrates were present in about 80% of biopsies (5).

Degenerative changes within muscle fibers may range from mild to severe. Early changes often consist of altered staining in the center of the fiber, visible on both hematoxylin-eosin and modified Gomori trichrome stained cryostat sections. Vacuolated fibers may be common, with the vacuoles commonly devoid of PAS+ (glycogen) or Sudan Black+ (lipid) material. Pale fibers, undergoing simple necrosis, are usually scattered throughout the biopsy. Other fibers may be filled with mononuclear cells, representing lymphocyte and macrophage invasion and phagocytosis (Fig. 1).

Inflammatory infiltrates consist of a mixture of large and small mononuclear cells, and may be found in the perimysial connective tissue, the endomysial connective tissue, or surrounding small to medium-sized venules or arterioles (Fig. 2). In a series of studies, Arahata and Engel (6–10) have shown that the majority of the mononuclear cells comprising the endomysial infiltrates consist of T cells, T8+ cells, and activated T cells, but rare B cells. In fibers undergoing phagocytosis, the invading cells are predominantly T8 cytotoxic cells, with relatively fewer macrophages (6).

A variety of relatively nonspecific changes may also be seen, especially with many of the histochemical reactions. Small, basophilic staining fibers, containing enlarged nuclei, may be present near areas of muscle fiber breakdown, and represent regenerating fibers. With the adenosinetriphosphatase (ATP'ase) reaction, fibers are often seen containing focal areas of inhibition of enzyme activity ("ghost fibers"). Small, angular, excessively dark fibers, demonstrated with the NADH-TR reaction, may repre-

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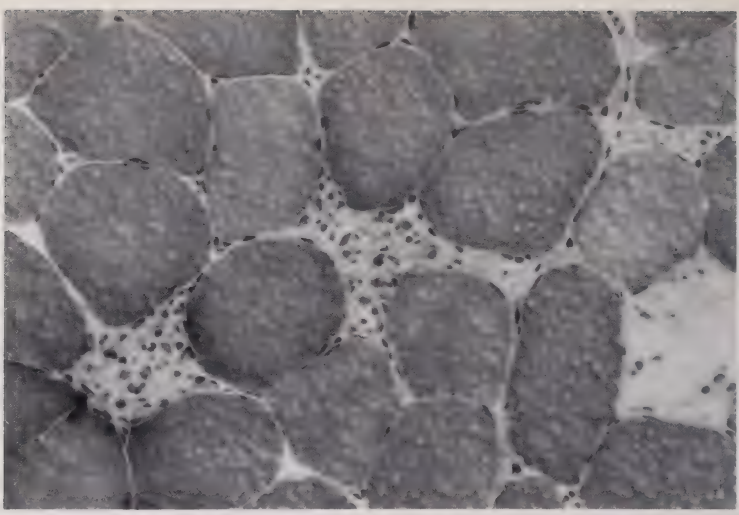

Fig. 1. Two fibers undergoing necrosis with phagocytosis; fiber on right of section undergoing simple necrosis (modified Gomori trichrome stain, original magnification 160×).

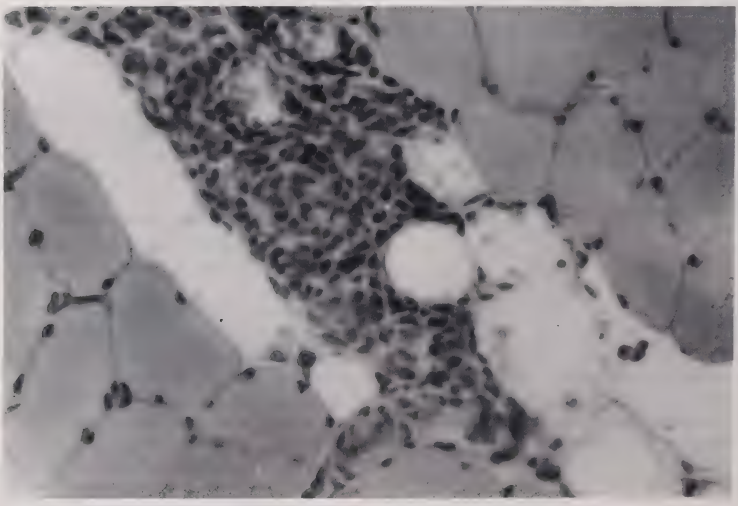

Fig. 2. Focal inflammatory infiltrate in perimysial connective tissue (hematoxylin-eosin stain, original magnification 160×).

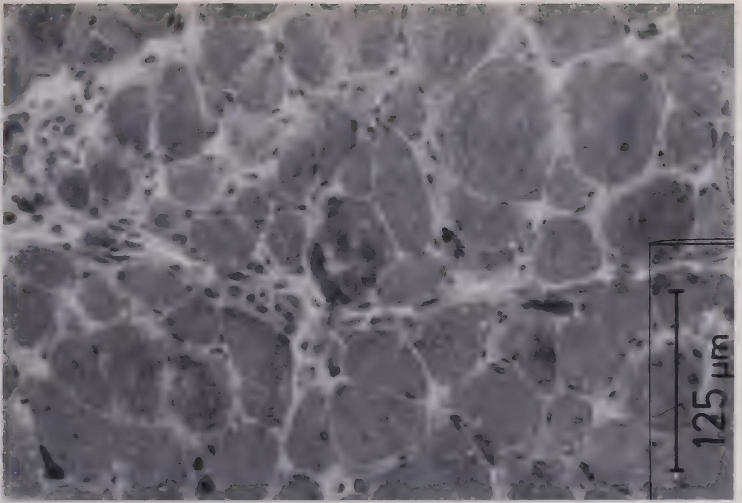

Fig. 3. Chronic myopathic changes in polymyositis, including increased variation in cross sectional diameter of muscle fibers, centrally located muscle fiber nuclei, slight endomysial inflammatory infiltrate, and mild proliferation of endomysial connective tissue (modified Gomori trichrome stain, original magnification 160 ×).

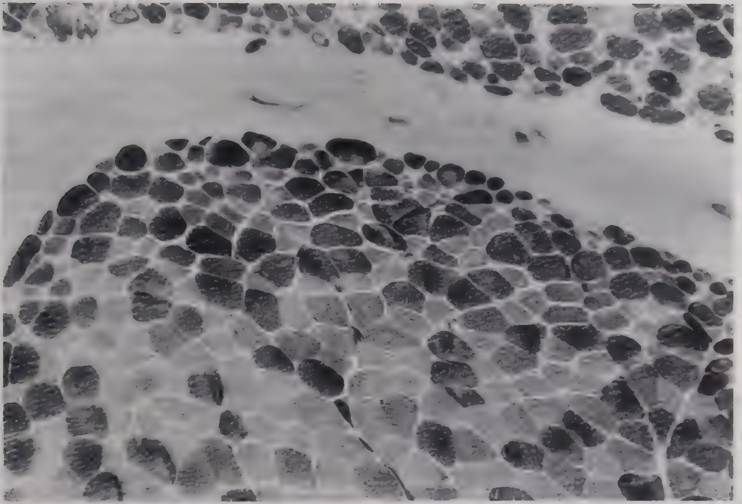

Fig. 4. Perifascicular atrophy in a child with dermatomyositis. Fibers in center of fascicle are normal in size, whereas majority of fibers bordering perimysial connective tissues are atrophic. In addition, some show focal areas of decreased enzyme activity (myofibrillar ATP'ase reaction, pH 9.4; original magnification 100 ×).

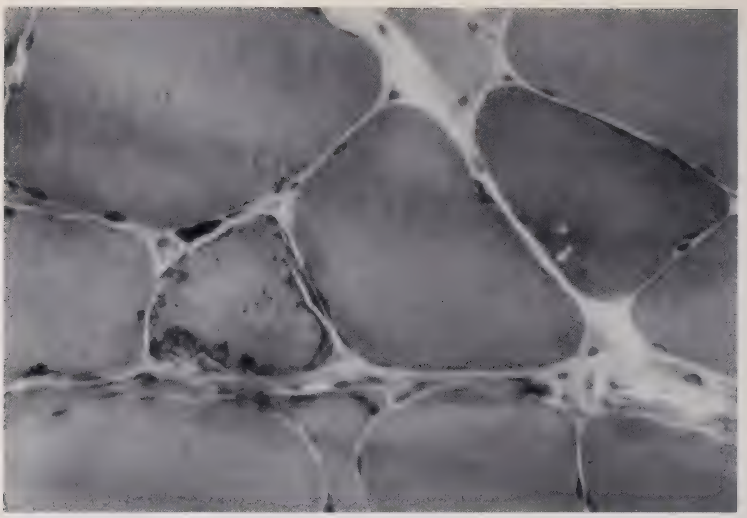

Fig. 5. Fiber containing subsarcolemmal vacuoles, rimmed with trichromatically stained material, from patient with inclusion-body myositis (modified Gomori trichrome stain, original magnification 400 ×).

sent an element of coexistent denervation atrophy, possibly resulting from involvement of intramuscular nerves (1).

In more chronic cases, muscle fiber hypertrophy and atrophy may be seen. Often proliferation of endomysial connective tissue occurs, with focal areas of fibrosis present (Fig. 3). In advanced cases, replacement of muscle by fat may occur.

The inflammatory infiltrate in mild and early cases may be quite focal. Sampling error in choosing a biopsy site may lead to failure to identify characteristic changes. If the clinical suspicion of polymyositis is strong, it may be necessary to cut multiple additional sections in a given block, or take sections from a second block if available, to help confirm the diagnosis pathologically.

Dermatomyositis

In many respects, the pathologic features of dermatomyositis are very similar to polymyositis. Endomysial and perivascular inflammatory infiltrates, fiber necrosis, and phagocytosis can all be seen in both adult and childhood dermatomyositis (1–5). In addition, a feature commonly seen in dermatomyositis is perifascicular atrophy, found only rarely in polymyositis. Biopsy specimens, oriented in cross section, will show relatively normal-appearing fibers in the center of fascicles, with varying amounts of atrophy affecting the fibers at the periphery of the fascicles (Fig. 4). The perifascicular changes often include vacuoles within fibers, scattered necrotic fibers, and alterations in pattern of histochemical reactions, including ATP'ase and oxidative reactions.

Although the etiology of the perifascicular changes is not clear, many workers feel it is the result of fiber ischemia secondary to blood-vessel changes. Banker and Victor (11, 12) detailed a variety of abnormalities in blood vessels from involved muscle in childhood dermatomyositis. Ultrastructural studies demonstrated endothelial degeneration and regeneration, the presence of tubular aggregates in endothelial cells, and endothelial hyperplasia. The effect of the vasculopathy is vascular thrombosis leading to muscle infarction. Similar changes can be found in vessels in other organs, including the bowel, leading to infarction there; skin; connective tissue; and nerves (4, 11).

Abnormalities involving circulating antibodies were demonstrated initially by Whitaker and Engel. In 9 of 11 children with dermatomyositis, Whitaker et al found deposits of IgG, IgM, or C3, on intramuscular blood vessels. These abnormalities were also noted in patients with adult dermatomyositis (3/12) and polymyositis (2/7), but were clearly less common in these entities. Subsequently Kissel et al (14) localized complement membrane attack complex to muscle microvasculature in 10/12 patients with childhood dermatomyositis. The presence of immune complex deposition in the blood vessels suggests a role for humoral immune mechanisms in the pathogenesis of the disease.

The cellular response in dermatomyositis differs from polymyositis in having a higher percentage of B cells. In biopsies from four children and two adults with dermatomyositis, 40% of the perivascular infiltrate consisted of B cells; 15% of the perimysial inflammatory cells were B cells; and 11% of the endomysial inflammatory cells were B cells (6). The presence of high proportions of B cells supports the hypothesis that humoral factors play a significant role in the pathology of dermatomyositis, whereas T cells are the primary immunoreactive cell in polymyositis.

Inclusion-Body Myositis

Although the entity now called inclusion-body myositis (IBM) was initially described by Chou (15), it remained largely ignored pathologically until the paper of Carpenter et al (16). In that publication, the characteristic rimmed vacuoles, visible on hematoxylin-eosin and Gomori trichrome stained cryostat sections, were emphasized as diagnostic criteria to differentiate the disease from typical polymyositis (Fig. 5). The vacuoles are not visible on formalin-fixed, paraffin-embedded material. Although the rimmed vacuoles are not specific for IBM (17), the presence of multiple fibers containing the vacuoles, in the setting of inflammatory infiltrates, necrosis and phagocytosis, and fiber atrophy and hypertrophy, is sufficient to make the diagnosis. Characteristic ultrastructural changes include the presence of 15–18 nm filaments, often located beneath the sarcolemma, and spheromembranous whorls.

Patients with IBM tend to be older males, have a slowly progressive disease with distal and proximal involvement, and do not respond well to corticosteroid treatment. The recognition pathologically of IBM in a patient with a suspected inflammatory myopathy is of importance to the clinician, especially in determining possible response to treatment. Long-term immunosuppressive therapy is not warranted, because of the generally poor clinical response. Failure to diagnose the disease may result in inappropriate treatment measures.

Summary

The pathological changes in polymyositis, dermatomyositis, and inclusion body myositis consist of perivascular, endomysial, and perimysial inflammatory infiltrates; muscle fiber necrosis and phagocytosis; and a variety of other degenerative changes, which individually are nonspecific. In polymyositis, the inflammatory infiltrate is T-cell dominated, representing a cellular immune attack directed against muscle. In dermatomyositis, vascular involvement is more prominent, with perifascicular atrophy nearly diagnostic of the disease. The inflammatory infiltrate has a much greater percentage of B-cell involvement than does polymyositis, and circulating immunoglobulins attached to blood vessels are common, especially in the childhood form. The characteristic lesion in inclusion body myositis is the presence of rimmed vacuoles, in the setting of inflammatory infiltrates, muscle necrosis, and often marked variation in muscle fiber cross sectional diameter.

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Electromyography in Idiopathic Myositis

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Electrodiagnosis plays an important role in the evaluation and management of patients with inflammatory muscle disease or myositis. Inflammatory myopathies can be divided into idiopathic and infectious types, and polymyositis constitutes the largest subset of the idiopathic form (Table 1) (1).

The cardinal feature of myositis is weakness. Diagnosis may be challenging because there are no reliable laboratory tests or unequivocal clinical findings (1, 2). Inflammatory changes on muscle biopsy are the most diagnostic sign, but because the distribution and temporal course vary markedly, a normal biopsy does not exclude the diagnosis (3).

The electrodiagnostic evaluation includes sensory and motor nerve conduction studies, evaluation of neuromuscular transmission, and needle electromyography (EMG). An important role often overlooked is the electromyographer's ability to exclude other disorders that may mimic myositis but require different treatment and have different prognoses. Electromyography is minimally invasive, and most of the evaluation can be quantified, especially using newer computer-based processing capabilities such as single-fiber EMG and automatic interference pattern analysis. Virtually any muscle can be studied, and examinations can be repeated to evaluate treatment.

The electrodiagnostic evaluation in suspected myositis is similar to the evaluation for any patient with weakness (Table 2). Electrodiagnostic abnormalities accurately reflect underlying pathologic changes, although the findings are not specific to the underlying cause. For a given muscle, the electromyographer may not be able to distinguish between idiopathic polymyositis, inclusion-body myositis, or even McArdle's disease. However, knowledge of the distribution of electrodiagnostic abnormalities and use of ancillary electrodiagnostic techniques may make these distinctions possible.

Electrodiagnostic Examination

Nerve Conduction Studies. Electrical responses can be recorded from sensory nerves and muscles following percutaneous peripheral nerve stimulation. Response measures include sensory nerve action potential (SNAP) and compound muscle action potential (CMAP) amplitude, terminal latency, and conduction velocity over a segment of nerve. Additional conduction studies include the F response and H reflex, both of which measure conduction over the most proximal nerve segment. The only expected conduction abnormality in myositis is a borderline-low CMAP amplitude recorded from a clinically weak muscle. This frequently involves the trapezius or biceps brachii muscle following stimulation of the spinal accessory or musculocutaneous nerves, respectively. Other conduction study results usually are normal. It is important that SNAPs be recorded in all patients with weakness because detection of subclinical sensory abnormalities may be important in excluding the diagnosis of myositis. Mild and slowly progressive sensory loss may go unnoticed by the patient and the examining physician.

Neuromuscular Transmission. Neuromuscular transmission can be evaluated by repetitive motor nerve stimulation at low rates (3 Hz). Defective transmission results in a decremental CMAP response, the initial response being the

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largest and subsequent responses being smaller. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome are two disorders that clinically may be confused with idiopathic myositis but are distinguishable by characteristic defects of neuromuscular transmission. Occasional patients with atypical motor neuron disease resemble patients with myositis. These patients also may demonstrate mild defects of neuromuscular transmission (related to reinnervation), but such abnormalities are atypical in myositis and should suggest an alternative diagnosis. Patients with myotonic dystrophy or myotonia congenita also may demonstrate a decremental response. This decrement does not relate to defective neuromuscular transmission but reflects a prolonged muscle refractory period. Because all of these disorders may demonstrate needle electromyography abnormalities that can be confused with myositis, repetitive motor nerve stimulation is an important component of the electrodiagnostic examination.

Needle Electromyography. Needle EMG, an extension of the neurologic examination, allows assessment of individual muscles. Sensitive at detecting subtle abnormalities, EMG may be markedly abnormal in patients with minimal or equivocal clinical findings. The EMG examination discriminates between neurogenic or myopathic disorders and may be useful in determining whether the disease process is ongoing or stable. Like nerve conduction and neuromuscular transmission studies, the EMG examination is particularly useful in excluding other causes of weakness such as peripheral neuropathy, motor neuron disease, mononeuritis multiplex, polyradiculopathy, many muscular dystrophies, and myopathies other than myositis.

EMG has been established as the most important electrodiagnostic component of the myositis evaluation; the triad of abnormal insertional activity, complex repetitive discharges, and myopathic motor unit action potentials (MUAPs) is considered the electrodiagnostic hallmark of myositis (4). In addition, results of EMG may define the distribution and degree of muscle involvement, especially using the newer quantitative techniques.

TABLE 1

Classification of Inflammatory Myopathy

Idiopathic
- Dermatomyositis
  - Childhood or juvenile
  - Adult
- Polymyositis
- Dermatomyositis or polymyositis associated with an underlying neoplasm
- Dermatomyositis or polymyositis associated with or part of connective-tissue disease (overlap group)
- Dermatomyositis or polymyositis associated with other disorders of unknown etiology
- Less common types
  - Inclusion-body myositis
  - Eosinophilic polymyositis
  - Localized nodular myositis
  - Proliferative myositis

Infectious
- Viral
- Parasitic
- Bacterial

Conventional EMG is performed using either a monopolar or concentric needle electrode. The concentric electrode is preferred over the monopolar electrode for the evaluation of suspected myositis for several reasons. First, detection of abnormal spontaneous activity is an important component of myositis. Monopolar electrodes are subject to wear, and spontaneous potentials occasionally can be generated from the electrode tip independent of biolectric activity, mimicking pathologic muscle potentials. Second, monopolar electrode wear may cause variability of the recording characteristics over the lifetime of the electrode. Because quantitative MUAP measures are important in establishing a diagnosis of myositis, these differences may make interpretation difficult. Finally, most published quantitative MUAP data are valid only for concentric EMG electrodes (5).

The monopolar needle may offer a relative advantage when there is concern about communicable diseases. The low cost of the monopolar

TABLE 2

Electrodiagnostic Protocol to Evaluate Myositis

Nerve Conduction Studies

Sural sensory

If sural equivocal:
- Opposite sural
- Median sensory

Ulnar motor; include F-response latency and repetitive supramaximal stimulation before and immediately after 4 sec of maximal voluntary exercise

Musculocutaneous or spinal accessory; include repetitive stimulation

If legs weaker and these motor study results normal:
- Peroneal or
- Femoral

Any identified abnormality requires further evaluation of suspected disorder

Needle EMG

Primarily unilateral examination, although one or two muscles on opposite side may be examined to demonstrate symmetry as long as they are not likely muscles for biopsy

Selected distal and proximal muscles, in upper and lower limbs, including paraspinal (e.g., biceps brachii; first dorsal interosseous; vastus lateralis; anterior tibialis; medial gastrocnemius; lumbar paraspinal)

If results equivocal, consider:
- Single fiber EMG to evaluate neuromuscular transmission and muscle-fiber density
- Quantitative interference pattern analysis (e.g., turns analysis)

Parentheses indicate recording site.

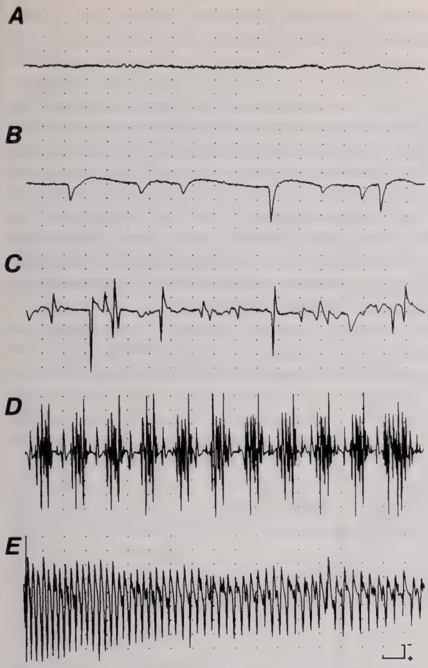

Fig. 1. Above Concentric needle EMG recording in muscle at rest. (A) Normal muscle with no spontaneous activity. (B) Abnormal spontaneous activity consisting of positive waves. (C) Fibrillation potentials and occasional positive waves. (D) Complex repetitive discharge firing rhythmically. (E) Myotonic discharge firing at a progressively slower frequency and lower amplitude. For A, B, and C: time marker, 10 msec; voltage marker, 50 μV. For D and E: time marker, 40 msec; voltage marker, 200 μV.

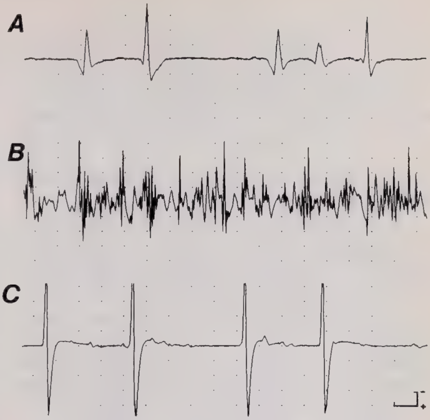

Fig. 2. Above Pattern of motor unit action potential (MUAP) recruitment at low levels of muscle force. (A) Normal recruitment with 3 MUAPs recruited. (B) Increased recruitment with many short duration polyphasic MUAPs despite low level of force, as seen in myositis. (C) Decreased recruitment with only 1 high-amplitude MUAP firing rapidly, as seen in neurogenic disorders. Time marker, 10 msec; voltage marker, 200 μV.

electrode makes it attractive as a disposable single-use electrode.

The EMG examination consists of the subjective, semiquantitative evaluation of insertional activity, abnormal spontaneous activity, and evaluation of MUAP recruitment and configuration.

Insertional and Spontaneous Activity. Muscle fibers displaced by movement of the needle electrode produce a burst of electrical activity, termed insertional activity, which subsides within 500 msec. In many neurogenic and myopathic disorders, including myositis, the muscle membrane demonstrates an abnormal electrical response to mechanical trauma. This "irritability" manifests itself by prolonged electrical activity after needle insertion (6). This nonspecific finding of increased insertional activity is indicated in a variety of ways, most commonly as unsustained positive waves. Conversely, many chronic disorders associated with increased connective tissue between muscle fascicles demonstrate reduced insertional activity, because connective tissue is electrically silent. In active myositis, increased insertional activity is a universal finding and virtually required to make the diagnosis. Endstage conditions with decreased insertional activity are less common and rarely observed in all muscles in a given patient.

Normal resting muscle is electrically silent after insertional activity subsides (Fig. 1A). In myositis, abnormal spontaneous activity consists of trains of positive waves, fibrillation potentials, and complex repetitive discharges.

Positive waves reflect spontaneous initiation of a muscle fiber action potential (MFAP) at the locus of the electrode. Because the potential always moves away from the electrode, it appears monophasic on the oscilloscope screen, resulting in the characteristic positive wave train (Fig. 1B).

Fibrillation potentials are similar to positive

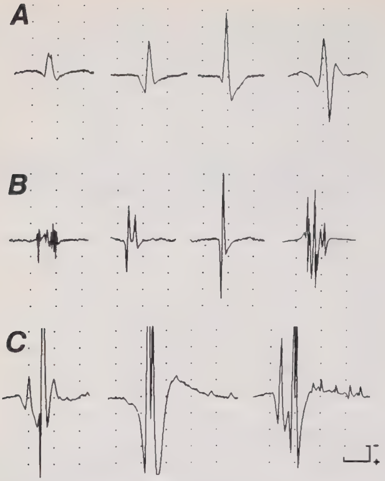

Fig. 3. Normal and abnormal motor unit action potential (MUAP) configurations. (A) Normal MUAPs. (B) Short duration, low to moderate amplitude, "spikey" and polyphasic MUAPs, as seen in myositis. (C) Large amplitude, long duration (including satellite potentials), polyphasic MUAPs, as seen in neurogenic disorders. Time marker, 10 msec; voltage marker, 200 μV.

waves but originate away from the electrode and reflect propagation of an MFAP along a single muscle fiber to and beyond the electrode. Because they originate distant to the electrode, fibrillation potentials usually are biphasic or triphasic (Fig. 1C). Both positive waves and fibrillation potentials represent a form of denervation hypersensitivity. Such potentials were initially felt to reflect only "neurogenic disorders." However, in myositis, necrosis of a muscle fiber segment serves to functionally "denervate" the portion of the fiber distal to the point of necrosis (7).

Complex repetitive discharges are involuntary, iterative discharges that occur in resting muscle (Fig. 1D). They initially were called bizarre high-frequency discharges or pseudomyotonia (because of their limited resemblance to myotonic discharges). Unlike myotonic discharges (Fig. 1E), these potentials do not wax and wane in frequency or amplitude. They typically begin and end abruptly and maintain a relatively constant discharge rate. Like other abnormal spontaneous activity, they are recorded in a variety of muscle and nerve disorders, including myositis. If true myotonic discharges are seen in a patient with suspected myositis, other disorders such as myotonic dystrophy, myotonia congenita, or hyperkalemic periodic paralysis should be considered.

MUAP Recruitment and Configuration. MUAP recruitment and configuration evaluation constitute the most subjective component of the EMG examination, being most dependent on the skill of the electromyographer. Force generated by a given muscle can be increased by increasing the individual MUAP discharge rate or by "recruiting" additional MUAPs. The latter is the primary method of increasing force. Motor unit recruitment reflects an orderly involuntary process, consisting initially of the discharge of smaller motor units, followed by subsequent recruitment of larger motor units (Fig. 2A) (8). In myopathy, the recruitment pattern is rapid, more MUAPs discharging than expected for a given level of force generated (Fig. 2B). This reflects the decreased number of functioning muscle

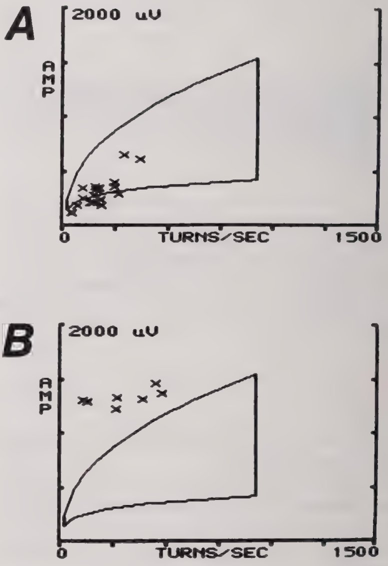

Fig. 4. Analyses of motor unit action potential (MUAP) interference pattern by measurement of number of turns (x axis) and their corresponding amplitudes (y axis) (see text for description). Curved triangle represents normal distribution of turns and amplitudes. X, individual observation. (A) Pattern seen in myositis, with many points lying below normal range, indicating many low amplitude turns; myopathic units. (B) Pattern seen in neurogenic disorders, with many points lying above normal range, indicating few turns of high amplitudes.

fibers. This can be contrasted to the decreased MUAP recruitment characteristic of neurogenic disorders, in which a decreased number of motor units are available (Fig. 2C).

The normal MUAP has a relatively simple and smooth triphasic configuration, representing the sum of individual MFAPs generated by the 5 to 12 local muscle fibers in a given motor unit (Fig. 3A). In myopathy, atrophic muscle fibers have smaller MFAP amplitude and therefore contribute less to the overall MUAP. In addition, individual fibers may degenerate and make no contribution to the overall MUAP. Following partial muscle necrosis with individual muscle loss and partial reinnervation of some atrophic segments, the resultant MUAP will be shorter in duration, lower in amplitude, and highly polyphasic, characteristics of the "myopathic" motor unit (Fig. 3B) (4). Exceptions to the short duration, low amplitude MUAP exist, most commonly in chronic myopathies when there may be substantial hypertrophy of individual muscles fibers and even extensive axonal sprouting of individual motor units with reinnervation of regenerating muscle fibers. This results in the paradoxical finding whereby a chronic myopathic process resembles a neurogenic disorder with larger amplitude MUAPs (Fig. 3B, far right).

Polyphasic MUAPs (defined as greater than four phases) commonly are recorded in both myopathic and neurogenic processes. The increased number of phases reflects accentuation of the underlying individual MFAPs that together make the MUAP. With reinnervation of muscle fibers by axonal sprouting, transmission along immature nerve fibers is slow, resulting in displacement of that MFAP from the summated CMAP. This results in more phases (polyphasia) and in extreme form isolated "satellite" potentials, commonly seen in myopathic and neurogenic disorders (Figs. 3B, 3C).

Single-Fiber EMG. Single-fiber EMG utilizes an electrode with a very small active recording surface, allowing the electromyographer to evaluate areas encompassing only one or two muscle fibers. When two neighbor muscle fibers from the same motor unit are recorded, the discharges are almost time-locked. The small amount of variability in timing between the MFAPs (referred to as jitter) reflects the slight variability in neuromuscular transmission. This very sensitive measure may be used in the evaluation of patients with myositis to quantitate abnormalities of neuromuscular transmission reflecting recent regeneration and reinnervation (11).

In addition, the single-fiber electrode can be used to measure muscle fiber density, a reflection of the number of muscle fibers belonging to the same motor unit within a given area. Increases in fiber density are not specific to myositis but are one of the most sensitive measures of muscle denervation (11).

Computer-Based, Quantified EMG. Several new computer-based EMG machines can make quantitative measures of the MUAP interference pattern. One approach involves quantification of the interference pattern, describing every point at which the EMG signal changes polarity as a turn, along with the corresponding amplitude between successive turns. A graphic display of the average amplitude versus the number of turns per second yields a series of points falling within a cluster in normal muscle (Fig. 4).

In myopathy, the large number of low amplitude, short duration, polyphasic MUAPs produces an interference pattern with many turns per second which have low amplitude (Fig. 4A). This contrasts with findings in neurogenic disorders, in which the large amplitude, long duration MUAPs produce many turns per second with large amplitude (Fig. 4B). This type of analysis provides objective, quantitative information about the time course of the interference pattern and frequently is useful in evaluating equivocal findings.

Discussion

Electrodiagnostic study of the patient with suspected myositis requires evaluation of sensory and motor conduction, neuromuscular transmission, and needle EMG. The nerve conduction and neuromuscular transmission studies are used primarily to exclude disorders other than myositis.

Nevertheless, the contribution of nerve conduction studies to the electrodiagnostic evaluation should not be underestimated. Frequently, patients with other forms of myopathy (metabolic myopathy, McArdle's disease, and so on), motor neuron disease (particularly the form associated with monoclonal gammopathy), proximal presentations of chronic inflammatory polyneuropathy, or myasthenia gravis share clinical features of myositis. In addition, patients with myasthenia gravis, often in the presence of a malignant thymoma, may simultaneously have defective neuromuscular transmission and electrodiagnostic and pathologic evidence of a superimposed inflammatory myopathy. Finally, sequential nerve conduction evaluations, recording CMAP amplitude in proximal muscles, may be used to follow the results of therapy in patients with inflammatory myositis.

Needle EMG remains the conventional method of evaluating patients with suspected myositis. However, the findings of abnormal spontaneous activity, complex repetitive discharges, and "myopathic" MUAPs are not pathognomonic of myositis. While all patients with active myositis demonstrate evidence of abnormal insertional and spontaneous activity, the distribution and patterns of these findings are of greater importance than their absolute presence.

Specifically, on EMG evaluation of the patient with myositis there is a predilection for proximal muscle involvement, the greatest abnormality being in paraspinal muscles (9, 10). Failure to demonstrate paraspinal muscle involvement makes the diagnosis of polymyositis suspect and may suggest another etiology. For example, asymmetric, multifocal EMG abnormalities with a distal predilection would be more characteristic of inclusion body myositis. Similarly, fulminant abnormalities without a proximal-to-distal gradient, in the proper clinical setting, would be more suggestive of an infectious myositis, such as trichinosis. Failure to demonstrate paraspinal muscle positive waves and fibrillation potentials, in an otherwise typical study, might raise the question of dystrophy or adult-onset McArdle's disease. Demonstration of an electrically silent cramp (contracture) following 30 sec of ischemic exercise would be highly suggestive of McArdle's disease, essentially excluding idiopathic myositis.

In prednisone-responsive patients with established myositis who subsequently deterioràte, a common question is whether the deterioration reflects an exacerbation of myositis or the development of steroid myopathy. In this context, the electrodiagnostic evaluation often can be helpful. The primary finding in steroid myopathy is normal spontaneous activity and rapid recruitment of relatively normal appearing MUAPs with no evidence of ongoing reinnervation. Thus, the patient with myositis receiving steroids who has increased weakness in a setting of minimal insertional abnormalities with no abnormal spontaneous activity strongly suggests steroid myopathy.

Another treatment-response measure relates to the amplitude of individual positive waves or fibrillation potentials. Following partial muscle fiber necrosis, fibrillation potentials average 100 to 200 μV in amplitude. In time, the "denervated" muscle fiber atrophies, and positive wave and fibrillation potential amplitudes also decrease. The presence of only small-amplitude positive waves or fibrillation potentials argues against ongoing muscle fiber necrosis.

The electromyographer may be helpful in determining the site for muscle biopsy. A biopsy should not be performed in a muscle recently studied electromyographically, because inflammatory changes are induced by the needle. However, the usual symmetric presentation of myositis allows the electromyographer to examine a muscle contralateral to the biopsy site to identify evidence of ongoing necrosis without endstage myopathic features or fibrosis. Biopsy of a clinically and electrodiagnostically uninvolved muscle is likely to be unrewarding; similarly, biopsy of a severely weakened muscle with electrodiagnostic evidence of fibrosis may be useless for accurate diagnosis.

In some patients, the performance of a needle examination results in an increase in the CK level and it is prudent to avoid making diagnostic CK determinations immediately after an EMG study.

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Juvenile Dermatomyositis

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In children, as in adults, chronic myositis must be differentiated from acute disease. Worldwide, most of the inflammatory myopathies (acute and chronic) are associated with bacterial or parasitic infections, whereas in North America viral myositis is more common. The spectrum of chronic inflammatory muscle disease includes both dermatomyositis (DMS) and polymyositis (PM). The pathognomonic skin manifestations aid in identification of juvenile dermatomyositis (JDMS); in polymyositis, the skin is spared.

The criterion of Bohan and Peter (1) establish the diagnosis: symmetrical proximal muscle weakness, elevation of muscle-derived enzymes in serum, evidence of inflammation on muscle biopsy or an abnormal electromyogram (EMG) with insertional irritability and bizarre foci of reactivity. The diagnosis of the disease is definite if, in addition to the rash, three of the four criteria are found; the diagnosis of polymyositis is definite if, in the absence of rash, three of the criteria are found.

Because myositis may be a component of other connective tissue diseases, it is essential to exclude children with conditions such as systemic lupus erythematosus, juvenile rheumatoid arthritis, mixed connective tissue disease and Sjogren's syndrome from research studies focusing on JDMS.

Epidemiology

As reviewed by Dr. Hochberg in this issue, the age distribution of PM-DMS is bimodal, the peaks being at 5–14 years and at 45–64 years (2). In the Midwestern United States, symptoms first appeared in the months of June–January in each of 7 years (1974–1980) in children who came to diagnosis within 4 months of onset of symptoms (3), suggesting a seasonal influence. There is some ambiguity about this point, for in a case-controlled study of 42 children with polymyositis (including an unknown number with JDMS) there was no difference in the season when the symptoms were first observed (4).

The frequency of disease is estimated to be 1–3.2 cases/1,000,000 in whites and 7.7 in blacks living in the United States. The typical rash is found in about 35% of all patients with chronic myositis, but JDMS is 10–20 times more frequent than PM in childhood (5). There is a female predominance of 2:1. In one study, children of African or Asian origin were more likely to have chronic myositis (6), but in the United States, white children with this disease have been reported more frequently than other racial groups (7, 8). Unlike some reports of cancer-related myositis, in children there does not appear to be any association of JDMS with malignancy. Overall, the greatest mortality appears to be in the nonwhite female patient group, and improved survival has been documented for those who are children (9).

Clinical Presentation

In JDMS, the rash may precede or follow the onset of proximal muscle weakness. Periorbital erythema and eyelid telangiectasia accompany periorbital edema in 50%–90% of affected children (10). Telangiectasia may persist long after other signs and symptoms of disease activity have resolved. The rash has a violaceous or heliotrope hue and is often most prominent on the eyelid, but may cross the bridge of the nose. The persistent rash may be elicited by brief sun exposure, with erythema involving the upper torso

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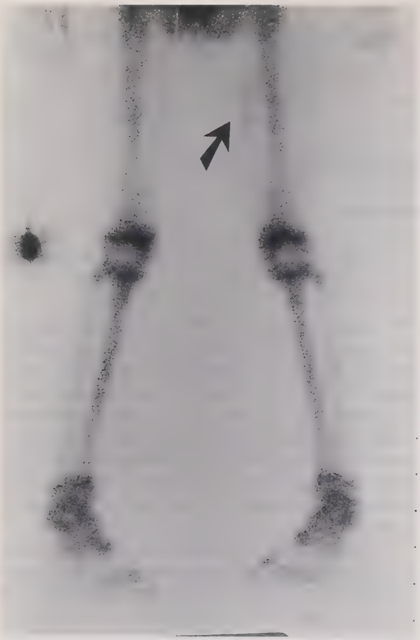

Fig. Uptake of technetium 99 in an area of vasculitis that did not demonstrate soft-tissue calcifications on radiograph.

and the extensor surface of the arms and legs, and may occur in the absence of elevation of serum levels of muscle-derived enzymes. Exposure to sunlight may cause exacerbation of skin inflammation alone, or may precipitate activation of the myositis as well. Recurrent photosensitive dermatitis has been found to precede muscle weakness in JDMS (11). The skin over the knuckles may be either hypertrophic or pale red, evolving into colorless bands of atrophic skin (Gottron's sign). Similar patches frequently occur over the elbows, knees, and medial malleoli of the ankles. Inflamed skin over the buttocks may make it difficult for the child to sit on a firm surface.

Diffuse vasculitis (nailbed telangiectasia, infarction of oral epithelium, skin folds, or digital ulceration) is clearly associated with more severe disease (12), and children with these symptoms may follow a nonremitting course which includes the development of soft-tissue calcification (13). Such calcifications, occuring in approximately ⅓ of children in some series (8) and in up to 70% in other series (14), are located at pressure points (knees, elbows, and buttocks) and appear to be a consequence of disease severity and duration (8).

Proximal muscle weakness, as evidenced by difficulty in climbing stairs, getting up from a chair, combing hair, or using hands to push off body in an attempt to stand (Gower's sign), is common; neck flexor weakness is a particularly sensitive indicator of muscle impairment.

Difficulty in handling secretions is usually associated with decreased esophageal motility (15) shown on radiographic contrast studies by persistent barium in a widened atonic pyriform fossa, the vallecular sign (16). An associated finding is nasal, high-pitched speech, which usually resolves with a decrease in the inflammatory component of the myositis; masseter involvement may be associated with difficulty in chewing food. The patient may not be able to swallow liquids comfortably. Esophageal reflux may result in aspiration pneumonia, and appropriate precautions should be employed to prevent this (for example thickened feeding, elevation of the head of the bed, bronchial drainage).

An abnormal electrocardiogram may be documented in over half the children with definite JDMS, an abnormality which is thought to resolve when the activity of the disease abates. Scanning with technetium 99 may reveal early sites of soft-tissue vasculitis, in addition to localized bone changes that herald early avascular necrosis (Fig.). A decrease in ventilatory capacity in the absence of respiratory complaints was found in 78% of children with definite JDMS (17). Pulmonary fibrosis may occur in both adults and children, but is more associated with those who develop antibody to Jo-1 and who have symptoms of overlap syndrome (18). The eye is also involved in JDMS, for in addition to thrombosis of vessels at the eyelid margin, "cotton-wool" spots have been reported as a result of small-vessel occlusion (19).

Pathophysiology

The vascular lesions can occur in the absence of a prominent inflammatory component (8) and, as stressed by Banker (20, 21), may be unique to children, although other investigators have found lesions in polymyositis that appear to be similar to those seen in JDMS (12). Capillaries, venules, and small arteries are damaged, with loss of muscle capillary network (12) and structural changes in the nailfold capillary bed (22). The primary lesion is in the endothelial cell, which contains reticulotubular inclusions and is the site of thrombosis and vessel obliteration; in some cases, increased collagen deposition in skin has been reported (14).

In plasma from patients with active disease, release of Factor VIII-related antigen (endothelial cell damage) and fibrinopeptide A (a measure of thrombin generation) has been documented during active disease, in conjunction with evidence, found by some investigators, of activation of the complement cascade, despite normal absolute levels of complement components (23). In addition, the C5b-9 membrane-attack complex has been localized in the intramuscular microvasculature of 10 of 12 patients with JDMS (24). The usual indicators of an acute phase reaction may be absent: sedimentation rate, white blood cell count, and differential cell count are often normal, but may be altered in persons with massive involvement.

Muscle pathology in JDMS reflects vascular compromise with perifascicular atrophy (25), equal involvement of Type I and Type II fibers (as opposed to steroid-induced myopathy, in which there is atrophy of Type II fibers), and inflammatory infiltrates of lymphocytes and plasma cells. In contrast, in PM, there appears to be less primary vessel involvement—vessels are normal in number and structure. In dermatomyositis, the infiltrate is composed of Ia+ B cells and an increased CD4/CD8 ratio. There appears to be a close relationship of CD4+ and B cells as well as macrophages, suggesting a humoral mechanism, perhaps directed against immune complex modified endothelial cells (26). Muscle-derived enzymes, creatine kinase (CK), aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT), and aldolase may all be elevated, or a single value may be abnormal (17).

Calcifications may resolve spontaneously, do not decrease when chelating agents are given (17), and are accompanied by increased urinary excretion of gamma-carboxyglutamic acid (GLA), which is a component of the vitamin K-dependent coagulation pathway (27). This increased GLA excretion (when compared to age and sex matched controls) was present both in the nine JDMS children who had no clinical or radiologic evidence of ectopic calcification (and whose mean values for GLA excretion were twice normal) and in the seven JDMS who did have soft-tissue calcifications (mean values three times normal). Routine measures of coagulation, including prothrombin time and activated partial thromboplastin time (17), are normal, but the perturbation of endothelial cells and thrombin generation may be linked in an as yet undefined manner to the increased urinary GLA excretion. The GLA-containing calcifications have the same diffraction pattern on x-ray crystallography as in scleroderma (28). The calcifications are not correlated with the presence of autoantibody, immune complexes, or known HLA antigens. Treatment with anticoagulants has been suggested (29), but has considerable hazard for the active child, and has not been proved to be effective in a case control study.

Genetic Studies

Reports of JDMS in more than one family member are sporadic, but the disease has occurred in monozygotic twins who developed muscle-related abnormalities 2 weeks after an upper-respiratory infection (30). The twins were HLA typed for ABC antigens, but not DR. In a large cross-sectional study of JDMS children and their families there was a marked increase in the white subjects of the HLA antigens B8 (relative risk 2.8, $P < 0.01$) and DR3 (relative risk 3.8, $P < 0.01$); in Latin Americans, the relative risk for DR3 was 18.5, $P < 0.05$, in the absence of abnormal HLA haplotypic segregation in 38 full siblings (7, 8). The association of the supratype A1, Cw7, B8, DR3 suggests that there might be a genetic component to disease susceptibility and expression.

Other autoimmune diseases associated with B8/DR3 include myasthenia gravis, type I (insulin-dependent) diabetes mellitus, and Grave's disease. Tests for a wide array of antibodies with tissue or organ specificity were negative when comparing 89 JDMS sera with 105 age and sex matched controls. Only the ANA and PM-1 were more frequent in JDMS patients than controls ($P < 0.005$ and 0.001, respectively) (31). There was no association with the presence of any other tissue- or organ-specific autoantibody and HLA B8/DR3 among white JDMS patients, documenting that in this group, B8/DR3 was not associated with generalized nonspecific autoimmunoreactivity (31).

The ANA positive sera from these children, unlike that from adults with myositis and pulmonary fibrosis, does not have specificity for the Jo-1 antigen (32) or Mi-2, found in adult DM (33). Furthermore, none of 39 JDMS sera recently tested for antibody to nuclear or cytoplasmic antigens had a nucleolar pattern on HEp2 substrate, and over 63% were positive at a titer greater than 1:80 in a pattern that was predominantly speckled (53%) rather than homogeneous (10%). None had antibody to cytoplasmic or cytoskeletal antigens (34). Assays for Scl-70, Ro/La,

TABLE

Tabulation of Coxsackie B Antibody Titers and HLA in Sera Taken from Chicago-Area Children with JDMS <4 Months of Onset

Patient number	Positive for			
	Complement-fixing antibody*	Neutralizing antibody†	HLA	
			B8	DR3
1	+	+	−	+
2	+	+	−	+
3	+	+	+	+
4	− (Plasma)	+	−	+
5	+	+	+	+
6	+	+	−	+
7	−	−	+	ND
8	+	+	+	+
9	+	+	+	ND
10	+	+	+	+
11	+	+	−	−
12	+	+	−	+
Total positive:	10/12	11/12	6/12	9/10

* Complement-fixing titers of eight or greater were considered positive.

† Neutralizing titers (ND_{50}) of 20 or greater were considered positive.

ND, not done.

anti-DNA, anti-RNP, and anti-DNP were all negative.

A possible infectious relationship is suggested by the observation that sera from newly diagnosed JDMS children from the Chicago area had increased frequency of antibody (both neutralizing and complement fixing) to coxsackievirus B (Table) as well as increased frequency of B8/DR3 (24). Studies are now in progress with Drs. M. Crowe and P. Plotz (NIH) with cDNA probes, using in situ hybridization, to determine if viral genome can be detected in muscle biopsies from those children with elevated neutralizing and complement-fixing antibodies to coxsackievirus B. In a recent report, an RNA probe identified coxsackievirus B2 persistence in muscle of 5 of 9 patients with PM/DM (one adult with PM, 4 children with JDMS), suggesting that this may be a fruitful approach to this problem (35). Other infectious agents, including *Toxoplasma* (36) and hepatitis B (37) have been considered. A study which combined electron microscopy and viral isolation documented that coxsackievirus A9 was associated with chronic myopathy (38). Coxsackievirus B2 was isolated from the stool and the CF titer of antibody rose in a child with chronic myositis (39). A rise in antibody titers to coxsackievirus B4 has also been documented (40).

Immunodeficiency

Dermatomyositis was associated with cerebral vasculitis in a 7-year-old boy with X-linked hypogammaglobulinemia (41) and it is now generally considered that those with hypogammaglobulinemia are at risk for echovirus "dermatomyositis." The onset is insidious; mild nonpitting edema of the lower legs is often the first sign of the disease (42). Unlike classical dermatomyositis, weakness is rarely a complaint; children recall stiffness in the elbows and knees which may precede or accompany neurologic symptoms. Muscle biopsy demonstrates mononuclear perivascular infiltrates which are thought to be mainly T cells, representing both helper and suppressor cytotoxic phenotypes; there is occasional focal calcification (43). A striking observation is that the child deficient in mature B cells is the most vulnerable. There is a predominance of X-linked males who have been culture-positive for echovirus (43).

Echovirus is a member of the human enteroviruses, which include the polioviruses, coxsackie viruses A and B, and those as yet unclassified except by number. Echovirus was cultured from 37 of 41 subjects with agammaglobulinemia, type 11 being the most common (11 cases) (44). Hypogammaglobulinemic patients have evidenced prolonged excretion of other members of the enterovirus group, such as coxsackievirus A15 in an infant (44), poliovirus after Sabin immunization (45), and echovirus type 3 (43), suggesting either inadequate clearance, or need for mature B cells in effective antigen presentation and response, or both.

Myositis has also been described in chronic graft-versus-host disease (46), but the muscle findings on histologic examination appear to differ from those of classical dermatomyositis (47).

Course and Therapy

Children have several types of disease course (monocyclic, recurrent, continuous), and it is difficult to predict outcome at the onset of illness (48), although some studies indicate that prognosis is a direct function of evidence of severe vasculitis (12, 13). Relapse in a child with an apparent monocyclic course is not common, but has been observed 8 years after apparent complete recovery from the initial insult (49), and there is sporadic evidence that despite apparent clinical quiescence, there may be continued histologic evidence of inflammatory muscle disease (50).

Before the advent of steroid therapy, a third of the children with JDMS died (51), but mortality has been reduced to about 7% since that treatment has been used (16). In patients with severe gastrointestinal involvement or vasculitis, intravenous administration of methylprednisolone is preferred until serum levels of muscle-derived enzymes have normalized. It is important to monitor for some known side effects of prednisone therapy: retardation of growth, changes in bone density, cataract formation, avascular necrosis of the femoral head. Occasionally, pulse doses of methylprednisolone may be useful (52), and some have suggested the use of methotrexate for children with refractory symptoms (53). A single case report suggests that intravenous gammaglobulin therapy may diminish disease activity (54), perhaps in a manner similar to that documented in Kawasaki's syndrome (55).

Graded physical therapy is very important to loosen contracted muscles. Local skin care and sun protection using blocking agents, as well as avoidance of strenuous exercise during the active phase of disease, all hasten recovery.

In the child with a deficiency of mature B cells, identification of the viral agent by lumbar puncture and culture is of great importance so that immunoglobulin containing high titers of the specific serotype can be administered intravenously (or on occasion by the intraventricular route) to achieve appropriate levels of neutralizing antibody (43).

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Temporal Association of Polymyositis-Dermatomyositis with Malignancy: Methodologic and Clinical Considerations

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The possible association of polymyositis or dermatomyositis (PM/DM) with malignancy was first described in 1916 (1, 2) and has since been reported frequently (3–14). Such temporal association has raised the possibility of a causal interrelationship between these disorders (6, 9–13). However, the validity of such reported associations has been questioned in a recent case-control study (15). The previous reports, therefore, should be reevaluated in the context of possible contributory biases (16, 17). If a true temporal association exists between PM/DM and malignancy, then diagnostic sensitivity to this relationship should be maintained and common host or etiologic factors should be investigated.

This article discusses (a) available data on the frequency of malignancy in patients with PM/DM; (b) potential biases which may create an association between these disorders; (c) possible etiologic relationships; and (d) cost-effectiveness of evaluation of PM/DM patients for malignancy.

Frequency of Malignancy in Patients with PM/DM

A recent review of the occurrence of malignancy in patients with adult-onset PM/DM, based upon 10 series published between 1977 and 1983, yielded an overall crude frequency of 13% (14). Such simple proportionate frequencies cannot be interpreted meaningfully unless proper comparison data are available. Over the years, the trend has been toward lower frequencies of concurrent malignancies. Earlier estimates ranged from 34% (4) to as high as 71% in males over 50 years of age (5).

Based on 13 series reporting frequencies of malignancy in adult-onset PM/DM and published since 1977 (Table 1), the overall crude frequency of malignancy was 20.4% in DM, 13.2% in PM, and 14.9% in all patients. Fisher's exact test comparing the proportion of malignancy in DM and PM was statistically significant (odds ratio 1.7, 95% confidence intervals 1.1, 2.6). However, no conclusion can be drawn from these data concerning an association of malignancy with PM/DM.

Biases and Biological Factors in Reported Associations

A bias in analytic research may be defined as "any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth" (17). Common biases as well as hypothetical biological factors may contribute to reported associations among diseases (Table 2).

Methodologic Pitfalls. Berkson's "paradox" indicates that persons with associated disorders are more likely to be admitted to hospital than those with only a single condition (29), especially if that condition is relatively asymptomatic. For example, a person with an occult malignancy and associated PM/DM has a greater likelihood of

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TABLE 1

Frequency of Malignancy in Adult-Onset PM/DM

Author(s) (Ref.)	DM	PM	Total*
Bohan A et al (18)	8/53	5/57	13/142
Scaling ST et al (19)	4/22	1/3	5/25
Callen JP et al (9)	7/27	1/31	8/58
Ogle S (20)	—	—	3/27
Henriksson KG & Sandstedt P (21)	3/19	4/51	7/86
Hersen S et al (22)	—	—	11/50
Black KA et al (23)	—	—	5/27
Hoffman GS et al (24)	1/7	1/12	2/27
Holden DJ et al (25)	4/10	0/18	4/36
Tymms KE & Webb J (26)	7/36	9/69	16/105
Manchul LA et al (27)	9/31	8/40	17/71
Hochberg MC et al (28)	3/24	3/34	6/76
Lackhanpal S et al (15)	11/50	18/65	29/115
Total cases (% with malignancy)	57/279 (20.4%)	50/380 (13.2%)	126/845 (14.9%)

* Total = DM + PM + connective-tissue diseases.

TABLE 2

Potential Biases and Biological Factors in Reported Disease Associations

Methodologic pitfalls
Berkson's bias of selective hospital admission
Differential ascertainment (diagnostic suspicion bias)
Selective case reports (positive results bias)
Uncontrolled series
Lack of specific diagnostic criteria
Hypothetical biological factors
Common host predispositions
Common toxic exposures
Other (immunologic, neurohumoral)

hospitalization than someone with a similar occult malignancy who does not have PM/DM (or another associated condition which is an indication for hospitalization). Hospitalization increases the chance of finding the occult malignancy above the normal population expectation.

Differential ascertainment bias (diagnostic suspicion bias) may further enhance a spurious association in retrospective analyses. Whereas Berkson's bias operates only on admission rates, ascertainment bias may influence both the intensity (15, 27) and the outcome of the diagnostic process (17). Hence, a temporal association may be created in hospital samples by virtue of the opportunity for selective admissions and differential diagnostic evaluation. Such biases may occur particularly in patients presenting to hospital with muscle weakness and weight loss (30), symptoms which occur both in PM/DM and malignancy. One can adjust for Berkson's and differential ascertainment biases by the proper choice of control conditions: those in which the likelihood of both hospitalization and diagnostic investigations to uncover malignancy are equal to that of PM/DM. Such controlled analysis may be achieved in a structured, longitudinal study, but none has been reported. In retrospective, hospital-based studies, however, such biases are more likely to exist and may create spurious associations between malignancy and PM/DM.

Selective case reports of two diseases, for example PM/DM and a malignancy (31), are interesting and are likely to be published, but have no statistical value. Similarly, reports of uncontrolled case series of PM/DM (Table 1) can raise suspicion of associations with malignancy but provide no scientific evidence for the association. However, properly conducted and analyzed case-control, hospital-based studies can provide useful data to address questions of disease association (16, 17, 32). Limited studies of this type are available on PM/DM and malignancy (15, 27).

Lack of specific diagnostic criteria for PM/DM or malignant neoplasms can introduce bias in determining the true association between these conditions. Because of a common belief that PM/DM is associated with malignancy, especially in persons over 40 years of age, less strict criteria may be applied to either condition when they are found in association.

Potential Biological Factors. Common host predispositions can contribute to an association between these disorders. An increased risk of both malignant lesions and PM/DM in older persons (14) can contribute to an association between these disorders. However, age adjustment or age-matching in case-control studies can minimize this effect. The association of PM/DM with malignancy has mainly been reported in persons aged 45 years or older. This finding may simply reflect the higher prevalence of malignancies in older groups. No critical studies of excess risk of this association has been reported in older versus younger adults (33).

Another potential host predisposition is sex. A greater likelihood of malignancy associated with PM/DM in adult men than in women was reported in 1962 (5). However, a 1985 review of 41 reported cases of PM/DM and malignancy revealed 27 (65.8%) among females, which is comparable to the 2:1 female-to-male ratio of PM/DM among adults (14). Sex-related factors do not seem to contribute importantly to an association between these disorders. The possible role of ethnicity deserves further study (7, 33, 34).

Common toxic exposures, for example smoking or alcohol use, may contribute to PM/DM and selected cancers, such as nasopharyngeal (33, 34) or lung (31, 33) malignancies. Persons exposed to such toxins may be more likely to acquire both conditions than those not so

TABLE 3

Design Features of Controlled Studies of Malignancies in Adult-Onset PM/DM

Study Design	Manchul LA et al (27)	Lakhanpal S et al (15)
Cases of PM/DM		
Number	71 cases over age 16	115 cases over age 18
Clinical classification	DM 31 (29 definite, 2 probable) PM 40 (17 definite, 15 probable, 8 possible)	PM 50, DM 65, all had muscle biopsy showing characteristic PM histology
Mean age (range)	50 (16–76)	52 (18–81)
Sex ratio	50 F/21 M	75 F/40 M
Reference or index date	First PM/DM admission to RDU	Initial PM/DM evaluation at Mayo Clinic
Controls		
Number	Group A: 71 pts Group B: 71 pts	115 carefully matched
Reference date	Admission	Evaluation
Mean age (range)	A: 52 (26–78)	52 (similar to cases)
Sex ratio	52 F/19M	75 F/40 M
	B: 51 (14–76)	
	50 F/21 M	
Methods		
Ascertaining malignant neoplasms	Chart review for antecedent and concurrent neoplasms. Follow-up for subsequent malignant neoplasms	Review of medical records, patient follow-up, selected review of death certificates; skin cancers not counted
Temporal classification of detected neoplasms	*Antecedent:* >6 mo before reference date	*Antecedent:* >30 days before index date
	Concurrent: ≦6 mo before or after reference date	*Concurrent:* ≦30 days before or after index date
	Subsequent: >6 mo after reference date	*Subsequent:* >30 days after index date

exposed, resulting in an indirect association between the diseases. Unless adjustment is made for such hypothetical toxic exposures, one might infer a direct, causal relationship rather than an indirect association between the two conditions.

No known HLA type or other genetic factor is believed to contribute to both PM/DM and malignancy, but the possibility deserves study (33). Hypersensitivity and disordered immunity have been suggested as a link between PM/DM and neoplasia (12, 35, 36). The possibility of PM/DM being a "paraneoplastic" reaction has also been raised (37, 38).

Possible Etiologic Relationships in Temporal Associations. Critical appraisal of malignancy in PM/DM versus other disorders needs to be divided into specified intervals related to time of diagnosis of PM/DM—antecedent, concurrent, and subsequent (7, 15, 27). Disease associations may be found at any or all of those intervals and would have different interpretations as well as different pathogenetic implications. Berkson's bias would operate most effectively in the concurrent-with-diagnosis interval. If significant excess of malignancy in PM/DM were found throughout all intervals in well-controlled studies, such data would argue against a simple, spurious association due to Berkson's bias, and might instead support a mechanism of common host predisposition or toxic exposures. A significant excess of malignancy in PM/DM patients found only in the antecedent and concurrent intervals would be consistent with ascertainment bias.

The fact that malignancy and PM/DM tend to increase with age among adults suggests that underlying host factors might contribute to an association between these disorders. Since the etiologies of these disorders are largely unknown, one can only speculate on mechanisms, at this stage.

Controlled Studies

Two recent case-control studies provide data on the frequency of documented malignant neoplasms in patients with PM/DM versus age- and sex-matched control groups (15, 27).

The University of Toronto Rheumatic Disease Unit (RDU) Study. In the study of Manchul et al (27), 71 patients over the age of 16 years with PM/DM were admitted to the Wellesley Hospital Rheumatic Disease Unit (RDU) between 1965 and 1980 and were followed up to 1981 (Table 3). Patients referred from a neighboring cancer research and treatment hospital were excluded. For each PM/DM case patient, two control patients were selected. The first control, in group A, consisted of the next patient admitted to the RDU with any disease other than PM/DM following the initial admission of the PM/DM case. The second control, in group B, consisted of an age- (±5 years) and sex-matched patient admitted to the RDU or Orthopedic Service with osteoarthritis, fracture, or fibrositis (that is, any noninflammatory conditions) within six months of the PM/DM case.

Diagnoses of malignant neoplasms antecedent to and concurrent with the respective case and control reference dates were ascertained by chart review. The authors indicated that clearly "a more intensive workup for neoplasms was done in patients with PM/DM, particularly those over 40 years of age, than in controls." Subsequent neoplasms were ascertained by an active follow-up process. In all patients, diagnoses of malignant neoplasms were confirmed by a pathology or autopsy report, a physician's letter, or a final hospital discharge note.

Antecedent malignant neoplasms were those diagnosed more than six months before the reference dates of PM/DM or control admissions. Concurrent neoplasms were those diagnosed within six months before or after the reference admission dates. Subsequent neoplasms were those diagnosed more than six months after the reference dates (Table 3).

Results of this study (Table 4) indicate that 15 (21.1%) of the 71 PM/DM patients had an antecedent or concurrent cancer found on chart review, compared to 4 (5.6%) of the 71 group A (RDU) controls and 1 (1.4%) of the 71 group B (noninflammatory) controls. One of the patients in each control group had basal-cell carcinoma, as opposed to no skin cancer among the cases. One patient subject had acute leukemia and another had fibrosarcoma, but the remaining neoplasms involved common epithelial sites. Statistical analysis confirmed the obvious differences between the frequency of antecedent and concurrent neoplasms in case and control groups. However, such a finding is of dubious value in view of the clearly recognized differences in intensity of work-up for such associated conditions among the study patients. Among the PM/DM subjects, no difference was found in the frequency of malignancy among females (24%) versus males (19%) or PM (17.5%) versus DM (25%). As expected, an association was found between the frequency of malignancy and age 40 years or older.

Analysis of subsequent malignant neoplasms revealed such diagnoses in 3 case patients versus 4 control patients in group A (RDU) and 5 control patients in group B (noninflammatory) (Table 4), obviously nonsignificant differences. The expected numbers of malignant neoplasms based

TABLE 4

Comparative Frequency of Malignant Neoplasms in Controlled Studies of Adult-Onset DM/PM

	Manchul LA et al (27)			Lakhanpal S et al (15)	
		Control Groups‡			
Temporal Intervals and Deaths	PM/DM† N = 71	A N = 71	B N = 71	PM/DM N = 115	Controls N = 115
	No. of patients diagnosed as having malignancy				
Antecedent	7	3	1	9	5
Concurrent	8	1	0	7	6
Subsequent	3	4	5	13	9
Expected subsequent neoplasms§	1.7	5.9			
First 3-yr follow-up after index date*				14	5
Subsequent total				13	9
thru 1 yr				3	0
thru 2 yr				7	1
thru 3 yr				8	2
No. deaths with malignancy**				20	10
	Malignancy per 100 person-years				
Subsequent total:‖	1.09	1.11	1.12	1.80	0.79
thru 1 yr				3.76	0.0
thru 2 yr*				4.63	0.56
thru 3 yr*				3.68	0.75
Death rates with malignancy**				2.74	0.88

* $p < 0.05$.

** $p < 0.01$.

† One PM/DM patient had two neoplasms antecedent to reference date and a third subsequent to it.

‡ One patient in each control group (A and B) had antecedent basal cell carcinoma as the malignant neoplasm.

§ Based on age- and sex-specific cancer rates in Canadian population.

‖ During the total subsequent period, PM/DM patients were followed 730 person-years and control patients 1,134 person-years, starting 1 mo after respective index date (15).

upon age- and sex-specific cancer rates from the Canadian population was 1.7 for case subjects (versus 3 observed), and 5.9 for the combined control groups (versus 9 observed). In both case subjects and controls, the ratio of observed to expected persons with neoplasms was greater than 1.0 (1.8 and 1.5, respectively) and may reflect the intensity of ascertainment of subsequent malignancies in the study groups. Subsequent malignant neoplasms occurred at a rate of 1.09 per 100 person-years (P-Y) among case subjects versus 1.11 among the RDU and 1.12 among the noninflammatory control patients (Table 4).

Failure to show a difference in subsequent malignant neoplasms between cases and controls may have been due to the limited power of the study and the fairly small number of person-years of follow-up of cases (274 P-Y), group A (RDU) controls (356 P-Y), and group B (noninflammatory) controls (433 P-Y). The power of the total study (cohort) was such that it had a 74% chance of showing a fourfold increase in cancer risk (and a lesser chance of finding smaller increases of cancer risk).

In conclusion, were this study not controlled, it would have provided data similar to previous reports of the frequency of malignancy in adult-onset PM/DM (Table 1) and would have further argued the long-suggested association of PM/DM and malignant neoplasms. However, by virtue of findings in the control groups, no evidence is provided for an increased risk of subsequent neoplasms. The differences found among subjects and controls in antecendent and concurrent malignancies may simply be a phenomenon of selective hospital admission and ascertainment bias, although other alternative and biological mechanisms cannot be excluded. The observation of 8 concurrent malignancies among the PM/DM subjects versus 1 among the group A (RDU) controls may suggest a subgroup of "carcinomatous myositis" patients which would not be expected to occur by chance.

The Mayo Clinic Study. In the study of Lakhanpal et al (15), 115 patients over the age of 18 years with histologically documented myositis were evaluated at the Mayo Clinic between 1965 and 1974 and followed up until October 1984 (Table 3). Patients with a primary diagnosis of malignancy or those who had their initial examination in the Department of Oncology were excluded.

For each PM/DM study subject, a control patient was selected from a computer listing of persons registered in the clinic of the same sex and similar age (±2 years), examined in the same clinical department during the same year (±1 year), and from the same geographic area of residence. In order to further match on duration of registration and length of medical follow-up in the clinic, the specific control patient was selected who had an identification number closest to the case subject.

Diagnoses of malignant neoplasms were ascertained by review of Mayo Clinic records, patient communication by letter and telephone interviews, as well as review of death certificates of patients reported dead of unknown cause. Skin cancers were not counted among the malignant neoplasms.

The authors indicated that PM/DM patient subjects had more extensive investigative work-up than controls, including barium studies, excretory urography, and mammography. However, those procedures were not believed to contribute to diagnoses of unrecognized neoplasms beyond what was suggested by a thorough clinical evaluation.

Antecedent malignant neoplasms were those detected more than 30 days before the index dates of the PM/DM or control evaluations. Concurrent neoplasms were those detected within 30 days before or after the index evaluation dates. Subsequent neoplasms were those detected more than 30 days after the index dates (Table 3).

Results of this study (Table 4) indicate that 29 (25.2%) of 115 PM/DM patient subjects had a diagnosis of malignancy at any time, compared to 20 (17.4%) of 115 controls ($P = 0.14$). One PM/DM and two control patients had two primary malignancies each. The temporal distribution of the detected malignant neoplasms in relation to the initial evaluations of PM/DM and control patients—their index dates (Fig. 1)—included antecedent neoplasms in 9 PM/DM and 5 control patients, concurrent neoplasms in 7 PM/DM and 6 control patients, and subsequent neoplasms in 13 PM/DM and 9 control patients (Table 4). Within the first 3 years after the index date, 14 PM/DM and 5 control patients were diagnosed to have malignant disease (Table 4, Fig. 1). Considering that PM/DM patients were followed 217 P-Y and controls 265 P-Y, during these respective "subsequent" intervals (personal communications), this difference is significant ($p < 0.05$) statistically (chi square 5.21, 1 *df*, Yates' correction and two-tailed test).

A personal communication from one of the authors of the Mayo Clinic study (LJM III) indicated that the cumulative incidences of malignant neoplasms from 31 days after evaluation through the 2-year and 3-year points (Fig. 2) are

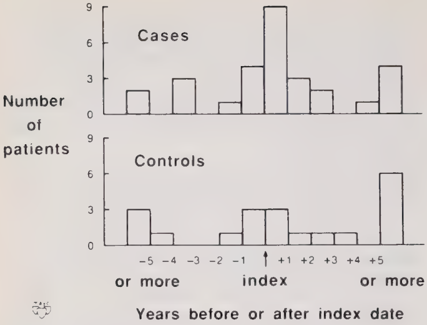

Fig. 1. Timing of diagnoses of malignant disease before and after date of evaluation (index date) in patients with polymyositis-dermatomyositis (cases) and controls. *Reprinted with permission from Lakhanpal S, Bunch TW, Ilstrup DM, Melton LJ III: Polymyositis-dermatomyositis and malignant lesions: does an association exist? Mayo Clin Proc 1986; 61:645–653.*

"significantly" greater in PM/DM subjects than in controls ($p < 0.05$). Such testing after inspection of the data (Table 4, Fig. 2) and finding the point(s) of greatest difference post hoc is not statistically valid and, therefore, was not done by the original authors. However, for purposes of this review, such testing identifies potential intervals in which a temporal association may exist between PM/DM and malignancy. An independent study would need to be performed to properly test such a hypothesis.

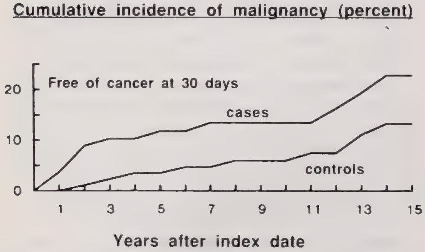

Fig. 2. Cumulative incidence of an initial malignant neoplasm among patients with polymyositis-dermatomyositis (cases) and controls who were free of cancer 30 days after evaluation. Note different incidences of acquired malignancies by end of second year among cases and controls (believed to have been free of cancer at 30 days following index date). Thereafter, curves are parallel and suggest no further increased risk of malignancy. *Reprinted with permission from Lakhanpal S, Bunch TW, Ilstrup DM, Melton LJ III: Polymyositis-dermatomyositis and malignant lesions: does an association exist? Mayo Clin Proc 1986; 61:645–653.*

Should a true excess of malignancy occur, further analysis of the types of cancer and referral patterns, among other variables, should be performed. The authors (15) identified a suggestive difference in the site of malignant neoplasms (7 lung cancers in subjects vs. 1 in controls) which may or may not be correlated to the "31st day to the 2- and 3-year" phenomenon. To the contrary, a relative excess of malignancies was reported among PM/DM subjects versus controls (6 versus 1) referred from the most distant geographic areas (rest of the U.S. excluding contiguous states and Canada), which occurred mainly in the antecedent interval. This observed difference by referral area may reflect biological mechanisms, selection bias, or chance but cannot explain the "31st day to the 2- or 3-year subsequent" phenomenon.

Death with malignant disease occurred in 20 PM/DM subjects and 10 control patients (Table 4). Considering the differential survival and follow-up of subjects (734 P-Y) and control (1,134 P-Y), the death rates with cancer per 100 P-Y are 2.74 in PM/DM and 0.88 in control patients (chi square 8.4, with Yates' correction, two-tailed $p < 0.01$). Whether or not morbidity associated with PM/DM may have hastened mortality with malignant disease in subjects as compared to controls is not known. Alternatively, PM/DM may be associated with an increased occurrence and mortality from malignancy.

The power of this study was estimated at an 80% chance to detect a fivefold difference in the incidence of malignancy using two-tailed probability. Because of the limited power, one cannot exclude the possibility of an association between PM/DM and malignancy in hospitalized patients, either at the fivefold or greater level (20% chance of nondetection) or lower levels (>20% chance of nondetection). In our review, two-tailed probability was also used in testing the null hypothesis. This is a more conservative approach than using one-tailed probability limits to test the alternate hypothesis that an association exists between PM/DM and malignancy. It may also tend to "counteract" effects caused by the various biases reviewed. Had the authors (15) used one-tailed probability, in the total "subsequent" interval a significant ($p < 0.05$) difference would have been found in the occurrence of malignant neoplasms per 100 P-Y between the PM/DM (1.80) and control (0.79) patients (Table 4). Whether or not a true biological association occurs in the population-at-large is another issue and cannot be determined exclusively from such hospital-based studies.

What These Studies Reveal. The Mayo Clinic study (15) is most informative by virtue of its relatively long follow-up of cases (730 P-Y) and controls (1,134 P-Y) and close matching process. Its definition of "concurrent" malignant neoplasms allowed only a two-month "window," whereas the "window" was a one-year interval in the study of Manchul et al (27). Accordingly, the latter study (27) may have uncovered a difference in concurrent malignant neoplasms between PM/DM and RDU controls (i.e., 8 versus 1), whereas the former study (15) seems to show a difference in early subsequent malignancies (that is, from the 31st day after evaluation through 2 years) between PM/DM and control patients.

Although each study had limited power, each one raises the possibility of an excess occurrence of malignancy around the time of initial hospitalization or within several years after the initial evaluation of PM/DM. The studies (15, 27) are rather consistent in their overall association of malignancies in PM/DM patients (25.2% and 21.1%, respectively). The subsequent malignant neoplasms per 100 person-years of total follow-up are also rather similar, considering the differences in definition.

Importantly, neither study excludes a temporal association between PM/DM and malignant neoplasms. To the contrary, during the concurrent and early-subsequent years, the available data are consistent with a subgroup of PM/DM patients having temporally associated malignant lesions.

Cost-Effectiveness of Evaluation for Malignancy in PM/DM Patients

Cost-effectiveness would not urge an intensive search for malignancy in all adult-onset PM/DM patients (9, 15, 24, 39), over all intervals. Rather, a carefully directed evaluation should be conducted in patients with (a) history of previous malignancy; (b) unexplained abnormal physical findings or laboratory tests; (c) positive findings, on review of systems, suggestive of malignancy; or (d) recent onset of myositis, not associated with an "overlap" connective-tissue disease, in a previously healthy middle-aged or older adult. Selective search and surveillance for associated malignancy may be appropriate under such circumstances, until results of further studies are available. Should the patient have dermatomyositis rather than polymyositis, be aged 45 years or older, and not have a good response to initial corticosteroid therapy in full dosage, then the probability of associated malignancy seems greater (14). Current data do not implicate an excessive risk of malignancy in PM/DM patients subsequent to two years following diagnosis (15), although such a possibility is not excluded.

Summary

Information reviewed suggests that a temporal association may exist between PM/DM and systemic carcinomas, but that it may occur within a limited time period of about 2 years and that the magnitude is not likely to be greater than fourfold or fivefold overall. However, statistical evidence is not currently available to either prove or disprove such a relationship. Based on the weight of available data, future well-designed studies would be justified in using one-tailed probability limits to test the alternate hypothesis of an increased incidence or frequency of malignancy in PM/DM. The null hypothesis that a decreased occurrence of malignancy in PM/DM is as likely as an increased occurrence is not supported by the available data.

Further controlled studies should be performed on the occurrence of malignancy in adult-onset PM/DM patients, especially those with a relatively short interval of several years between both diagnoses. Critical comparison of PM/DM patients with and without associated malignancy is also needed. Since malignancy risk increases into the oldest ages, whereas PM/DM tends to peak in the late-middle ages (40), the likelihood is that a diagnosis of PM/DM will precede a systemic malignancy, assuming sufficient follow-up. Except for immunosuppressive therapy of PM/DM, no direct linkage with subsequent malignancy is currently suspected. However, as yet undefined immunologic or metabolic processes, occurring in an "occult" malignant process, may precipitate PM/DM, thereby contributing to a limited temporal association. Future studies should be directed toward (a) more accurately defining the risk period of such possible association and (b) delineating possible mechanisms of association of malignancy with PM/DM.

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The Heart in Polymyositis And Dermatomyositis

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Cardiac abnormalities in polymyositis/dermatomyositis (PMS/DMS) are relatively common (1). Although not widely appreciated previously, these complications can be found in high frequency if conventional as well as contemporary noninvasive methods are systematically utilized (2). In addition to routine electrocardiogram and chest x-ray, echocardiography (3), 24-hour Holter monitoring of cardiac functions (4), thallium 201 scanning of the myocardium (5), ejection fraction and cardiac wall motion (6) studies are other methods that can be utilized in such studies. Cardiac catheterization is occasionally indicated in patients in whom the results of the electrocardiogram or Holter monitor indicate significant changes that raise the possibility of coronary artery disease.

A significant predictive factor indicating cardiac involvement in PMS/DMS is elevation of creatine kinase (CK) MB fraction, a study readily available in all laboratories (7). The presence of serum antibodies to tissue ribonucleoproteins as a marker for heart involvement in PMS/DMS has been recently investigated. The presence of antibody in 60% of patients with PMS/DMS and 70% in those with cardiac involvement indicates a relatively sensitive immunologic marker which may complement the CK-MB study (8).

Elevation of CK with or without elevation of aldolase is one of the criteria in the diagnosis of PMS/DMS (9). Isoenzyme studies in such patients indicate that most of the CK fraction is MM (muscle), MB (heart) fraction being elevated in a controversially different proportion of patients (2). Usually there is poor to fair correlation between the total level of serum CK and cardiac involvement. But level of CK-MB isoenzyme usually correlates with cardiac involvement if it is above 3% of the total CK (1, 2).

Although CK-MB of noncardiac origin is being reported in a number of neuromuscular diseases (10), in alcoholic rhabdomyolysis (11), and in strenuous physical exercise (12), CK-MB of cardiac origin without cardiac involvement is reported in PMS/DMS (13). A critical evaluation of such records, however, indicates some discrepancies in the conclusions drawn. For example, CK-MB was not significantly elevated (that is, was not more than 3%) in one of the patients reported by Larca (13), and two other patients had limited cardiac studies and short term follow-up. In general, the presence of elevated CK-MB fraction over 3% has indicated cardiac involvement in PMS/DMS, just as persistently elevated CK-MB has correlated with the severity of myocarditis or myocardial involvement and poor prognosis in this disease (1, 2). In fact, persistent elevation of CK-MB has been associated with fatal congestive heart failure in our observations (1, 2). Not systematically evaluated in PMS/DMS, the presence of MB isoenzyme has been regularly correlated with myocarditis in both lupus erythematosus (14) and scleroderma (15).

Myocardial histopathologic findings are usually reported at postmortem studies (16, 17) but a limited number of myocardial biopsies (18) are also available and both have indicated myocardial inflammatory and degenerative changes similar to skeletal muscles in PMS/DMS. Haupt and Hutchins (17) reviewed the clinical records of 16 autopsy patients with PMS/DMS and found that 7 patients had congestive heart failure, of whom 5 had myocarditis. Denbow (16), in review of 20 autopsy cases with PMS/DMS, found 6 pa-

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tients with clear evidence of myocarditis who did not have any significant clinical evidence of heart disease. The pathologic changes in the myocardium have consisted of inflammatory cell infiltrates, necrosis and fibrosis of cardiac muscles and conducting system, and a variety of vasculopathies in coronary arteries.

Although postmortem studies clearly have indicated significant cardiac changes due to PMS/DMS (16, 17), clinical evaluation of the cardiac abnormalities have been hampered by limited diagnostic methods, the number of patients studied (some of whom could have had other connective-tissue disease), lack of correlation between the findings with the CK-MB fraction, and the lack of report on the course of patients (19–23).

We recently utilized all available conventional and contemporary methods of cardiac evaluation in patients with PMS/DMS and here review our findings as they relate to each method, considering also the reports from the literature (1, 2).

Methods of Cardiac Evaluation

ECG. Routine electrocardiograms (ECG) show a variety of atrioventricular blocks, bundle branch blocks, premature atrial and ventricular contractions, and ST-T wave changes at times similar to myocardial ischemia or infarction (1, 2, 24–26). Such diagnoses, however, could be excluded by coronary angiography. The use of other noninvasive diagnostic methods, or the response of the patients to corticosteroids with the disappearance of ST-T wave changes, may prove to be satisfactory and eliminate the need for cardiac catheterizations. Whereas patients with PMS/DMS may have ECGs similar to myocardial infarction, some patients with clinical diagnosis of myocardial infarction might have undetected PMS. In general, routine ECG might be suggestive of but not representative of the full extent of the disease process.

Holter Monitoring. Holter monitoring (continuous electrocardiography) is a sensitive indicator of cardiac arrhythmias, found at times in patients who are otherwise asymptomatic or who have normal ECGs. These findings include paroxysmal atrial and supraventricular tachycardia, ventricular tachycardia, and a number of other arrhythmias, such as bigeminy pattern and sick sinus syndrome. Since this monitoring is not done systematically in all studies, the incidence of arrhythmias in PMS/DMS is unclear. In other connective-tissue diseases, such as scleroderma (27), continuing electrocardiography has indicated the presence of heart disease more extensive than that disclosed by routine ECG. How often serious cardiac arrhythmias have contributed to morbidity and mortality in PMS/DMS is unclear, but I suggest that Holter monitoring be included in the clinical evaluation of such patients, particularly in those who have elevated CK-MB fraction or those who demonstrate any abnormal findings on ECG.

Echocardiograms. Echocardiograms have indicated a significantly high prevalence of mitral valve prolapse (in about 65% of patients) and increased cardiac performance in the absence of any hyperdynamic state (19, 28). Contrary to other connective-tissue diseases in which echocardiography has revealed pericarditis rather frequently (29), PMS/DMS is less commonly associated with pericarditis or pericardial effusion (2, 19). Although mitral valve prolapse could be explained on the basis of cardiac necrosis due to PMS/DMS and dysfunction of cordae tendonae, reasons for increased cardiac function are less convincing (19, 28). In view of the valuable information in relation to the left ventricular dysfunction, hyperkinetic septal motion, and occasional presence of pericardial fluid, echocardiography should be considered in the cardiac study of all patients with PMS/DMS.

Thallium 201 Scan. Resting myocardial perfusion scintigraphy after administration of thallium 201 (5) may disclose underperfused areas indistinguishable from myocardial infarction (1, 2). The underperfused areas of the myocardium usually correlate with other findings such as echocardiography and gated blood pool studies. Confirmation of PMS/DMS rather than myocardial infarction could be achieved by the fact that exercise should not affect thallium scans in PMS and that abnormal findings may resolve after treatment with corticosteroids (1, 2). Although not previously reported in PMS/DMS, abnormal resting thallium scans and perfusion studies have been observed in congestive cardiomyopathy (30) and sarcoid heart disease (31). The underperfused foci by thallium 201 scans in PMS/DMS correlate with pathologic findings of myocardial necrosis reported on postmortem studies (16, 17).

Gated Blood Pool and Ejection Fraction Studies. Gated blood pool studies and ejection fraction may indicate akinetic areas (5) and, if correlated with findings on echocardiogram and thallium 201 scanning, confirm the possibility of myocarditis. In the absence of coronary artery disease, akinetic or hypokinetic ventricular wall motion appears to be the result of focal involvement of the myocardium by PMS/DMS. The relative severity of myocarditis can be indicated by a significantly decreased ejection fraction, as I concluded in my study (1, 2).

Angiography. Coronary angiography (1, 2, 25) may be occasionally needed in patients with an abnormal ECG that demonstrates changes consistent with myocardial ischemia or infarction. Such studies may reveal findings consistent with arteritis obliterans, inflammatory changes consistent with vasculitis, or normal findings in spite of changes on routine ECG (25). If one proceeds with angiography, an endomyocardial biopsy could be obtained for confirmation of the disease (18).

Utilizing these methods of cardiac evaluation, some degree of cardiac abnormality is found in most if not all patients with PMS/DMS. Whereas the Holter monitor may detect supraventricular tachycardia in the presence of otherwise normal studies, the echocardiogram and perfusion studies may disclose significant changes despite unimpressive findings by Holter monitor (1). Thus each method of evaluation complements the others, and unless the physician is convinced of the extent of myocardial involvement in a patient with PMS, all methods should be utilized.

Treatment and Prognosis

Cardiac abnormalities usually respond to the conventional treatment of PMS/DMS with prednisone, 60–80 mg/day for 6–8 weeks (32). In fact, many abnormalities found by ECG, Holter monitor, or cardiac wall motion study may resolve after the treatment is initiated (1, 2). Patients with persistent PMS/DMS who do not respond to conventional doses of corticosteroids may fail to respond to immunosuppressives as well (20, 22, 33). Although the general clinical assessment of PMS/DMS can be achieved by manual and functional muscle examinations as well as by measuring total serum CK and urine excretion of creatine, cardiac management may require periodic reevaluation of the cardiac laboratory methods which were utilized at the onset of the disease, particularly those showing abnormalities. Symptomatic cardiac arrhythmias may require antiarrhythmic drugs; congestive heart failure may indicate treatment with diuretics and/or digitalis; and symptomatic heart block may require implantation of pacemakers. Pericarditis, although not common, may readily respond to treatment with corticosteroids, an outcome which could be evaluated by periodic echocardiograms until complete resolution of pericardial effusion (34).

Cardiac involvement appears to be associated with a worse prognosis of PMS/DMS (1, 2, 20, 35–37) even in the absence of its correlation with severity of the disease as indicated by functional class of the patient (38). In my own series, one of the two deaths in patients with PMS/DMS could have been attributed to cardiac involvement and congestive heart failure which developed in two patients who required numerous hospitalizations for cardiac complications (1, 2). Sharratt, Danta, and Carson (21) compared the course of 5 patients exhibiting myocardial involvement with 8 patients without cardiac involvement of PMS/DMS and found a longer history of persistently active myositis and more severe disease in patients with cardiac involvement. Other investigators have confirmed the findings of Sharratt, observing more serious morbidity and mortality in patients with PMS and cardiac involvement (28). A graver prognosis was also observed by Oka and Raasakka (20) in 11 of 16 patients with cardiac involvement; congestive cardiac failure was prognostically worse compared with other cardiac findings.

In summary, cardiac abnormalities in PMS/DMS are not uncommon. The previously unappreciated frequency of such abnormalities is mainly related to the limited methods of evaluation. Utilizing conventional methods such as echocardiography, Holter monitoring, thallium 201 scanning, and gated blood pool studies, one may find a significantly higher frequency of cardiac involvement. In my own experience, all patients with elevated CK-MB had at least one, and most of the time several, abnormalities. Although the total CK level had a fair correlation with cardiac involvement, the presence of MB fraction over 3% invariably indicated cardiac abnormality which was confirmed by systematic studies. Routine ECG can indicate abnormalities such as ectopic beats, conduction abnormalities, and at times ischemic changes undifferentiable from myocardial infarction. Holter monitoring may demonstrate significant arrhythmias in some cases, at times unexpectedly. Thallium 201 scintiscanning and gated blood pool studies are complementary to echocardiography and are used in demonstrating overall cardiac performance of akinetic or hypokinetic wall motion, the presence of pericardial effusion, and mitral valve prolapse, which all were prognostically important findings. Corticosteroids appear to be the mainstay of treatment, but occasionally specific treatments for cardiac arrhythmias or congestive heart failure may be required. On follow-up, in addition to the regular evaluation of PMS/DMS, specific cardiac studies may be required. In patients with severe cases not responding to corticosteroids, immunosuppressives such as Imuran may fail to improve the cardiac abnormalities.

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The Therapy of Polymyositis

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Corticosteroids

ACTH and corticosteroids were introduced for the treatment of polymyositis not long after the discovery of cortisone and were found to be beneficial (1, 2). Although no controlled prospective trial with corticosteroids has been carried out in polymyositis, nor should one now, the overwhelming evidence from retrospective analysis indicates its usefulness, especially in lessening pain and weakness. Prior to the introduction of corticosteroids into treatment, many different forms of therapy were tried, including testosterone, vitamin E, thyroid and antithyroid drugs, insulin, iodine, and PABA (3).

From 1950 to about 1960, cortisone was used in small doses or not at all. One commonly cited paper, for example, which compared "high-dose" to "low-dose" cortisone, was actually comparing a 50-mg dosage to a 10-mg dosage, which today would be considered too low (4). In about 1960, higher doses of prednisone began to be used, and a review paper in 1963 documented high-dose prednisone, 40–60 mg/day, as standard therapy (5).

The evidence, albeit mostly retrospective, strongly supports the use of high-dose (greater than 40 mg/day) prednisone as soon as possible in order to minimize disability. In one study, 24 of 30 patients improved one grade of disability over the first three months of therapy on a dosage greater than 40 mg/day, whereas only six improved one grade on a dosage of 20–40 mg/day (6). In another large study, the degree of improvement in the first three months was proportional to the dosage of prednisone; therefore larger doses (⩾40 mg a day) were recommended early in the treatment course (7). Papers from the Newcastle group in England generally support a regimen of early high-dose prednisone also (8–10).

Over a longer time, most patients slowly improve. One long-term follow-up study noted 60% disability at one year, 40% at five years, and 20% at ten years (10). A prospective study found an improvement of about one grade in disability in one year and an improvement of two grades by three years (11). In a large retrospective study, 50% were better at five years, and 80% of these patients had little disability (7). In contrast to these studies at tertiary-care institutions, a rural community hospital study of polymyositis patients noted that 64% improved after just three months, and a surprising 41% were able to discontinue all therapy. Thirty-eight percent were treated with every-other-day prednisone (12).

Generally, an every-other-day dosage is not recommended early in the course of treatment but may be acceptable later. Seventy-five percent of patients in one study could eventually be managed on an every-other-day dosage with no noticeable worsening or even with some improvement (6). Dosages of prednisone required to keep polymyositis under control usually lessen with time from 40–60 mg for the first three months to 10–15 mg at one year and <10 mg at three years (11).

Mortality. Mortality rates vary widely from study to study. A 50% mortality rate was noted in an untreated (that is, no cortisone) group studied in 1940 (13). In two large groups of polymyositis patients in whom cancer had been ruled out, there was no significant difference in mortality rate between the group treated with high-dose prednisone and the group untreated or treated with a low dose (14). At five years the mortality rate averaged about 20%. Other mortality rates, some including cancer patients, have ranged from 14% to 40% (6, 15).

Steroid Myopathy. Prednisone therapy can cause a number of unwanted effects. One that is

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TABLE
Criteria for Steroid Resistance in Polymyositis Active Disease as Indicated by Increased CPK, EMG, or Muscle Biopsy

Time on prednisone	Prednisone dosage/day
⩾3 mo	⩾60 mg
⩾6 mo	⩾40 mg
⩾9 mo	⩾30 mg
⩾12 mo	⩾20 mg

particularly distressing in polymyositis is steroid myopathy, since the last thing such patients need is an additional muscle problem. Studies in rabbits have shown the typical feature of steroid myopathy: type II (white) fiber atrophy (16). A study in humans, with follow-up biopsies at three months, showed that this development is more common in women and can develop fairly early in the course of treatment (14). Patients commonly have normal CPKs, a myopathic EMG without fibrillation potentials, and increasing weakness which improves with a decrease in prednisone dosage.

Steroid Resistance. Infrequently, patients do not respond adequately to prednisone (steroid resistance), and other drug therapy must be considered. In an attempt to standardize the concept of steroid resistance, guidelines have been suggested (17) and the Table presents them in an updated version.

Immunosuppressives

Use of immunosuppressives in polymyositis occurs in one of two settings, either de nouveau in combination with prednisone at the beginning of therapy or later, in steroid-resistant patients.

Azathioprine. Azathioprine has been shown to be effective in polymyositis when used with prednisone when treatment begins (11). A prospective controlled trial of azathioprine plus prednisone showed little or no added benefit when compared to prednisone alone over the first three months of treatment (18). After one year, however, and especially after three years, the combination of prednisone and azathioprine was superior to prednisone alone, as judged by disability levels and doses of prednisone necessary to control the disease (11). In a retrospective study, it was noted that the addition of azathioprine to the regimen of steroid-resistant patients resulted in one grade of disability improvement in 35%, whereas 65% remained the same or grew worse (6). Fifty percent were able to decrease their prednisone dosage an average of 18 mg/day.

Azathioprine has proven to be a relatively safe drug. Monthly checks of hemoglobin, white blood cell count, platelet count, and alkaline phosphatase are recommended to monitor for bone-marrow or hepatic toxicity. Side effects are generally dose related. If dosages of 2 mg/kg per day or less are used, side effects are minimal. Occasionally, a patient will develop hepatic fibrosis in spite of low-dose azathioprine, or even when the alkaline phosphatase levels remain normal; such patients, fortunately, are rare. An occasional patient will develop lung toxicity, which usually improves with discontinuation of the drug. Nausea and other gatrointestinal complaints are generally associated with higher doses, although an occasional patient is intolerant of azathioprine even at 2 mg/kg per day.

Methotrexate. Methotrexate has also been shown to be effective in steroid-resistant patients. An uncontrolled prospective trial of 22 patients given intravenous methotrexate demonstrated effectiveness in 17 by allowing CPK levels to return to normal in an average of about 10 weeks (19). Side effects occurred in about 60%, but most of these were stomatitis and were reversible if the medication was discontinued either temporarily or permanently. Dosages range generally from 25 mg to 35 mg intravenously each week.

A retrospective study in 25 patients who did not respond adequately to prednisone alone showed that 64% of patients on methotrexate intravenously each week improved one grade of disability (6). Forty-two percent averaged a drop in prednisone requirement of 25 mg/day. The intravenous methotrexate dosage averaged 40 mg/week.

Others. In general, other immunosuppressives have not proven to be very efficacious or have not been adequately studied, but a combination of chlorambucil and methotrexate was shown to be successful in managing two patients with refractory myositis who had failed treatment with prednisone and high-dose intravenous methotrexate (20). On a regimen of prednisone 60 mg/day, oral methotrexate 15 mg/week, and chlorambucil 6 mg/day, one patient improved significantly. Another patient received chlorambucil 6 mg a day in place of azathioprine; later, 15 mg of methotrexate was added orally, along with 35 mg prednisone. In two months her previously refractory CPK levels returned to normal and remained so over a one-year follow-up.

Other Treatments

Plasmapheresis has been suggested as another form of therapy for polymyositis. Although no controlled trial has been carried out, in one study of 35 patients, either chlorambucil or cyclophosphamide was added at the same time as the plasmapheresis therapy (21). It was difficult to tell whether one drug, the plasmapheresis, or the combination was useful, but the patients seemed to improve.

Two cases of refractory polymyositis treated with total body irradiation have been reported. One patient had been unresponsive to prednisone alone and later also to azathioprine, methotrexate, and cyclophosphamide. After 150 rads of total body irradiation over five weeks (two 15-rad treatments each week) the patient's strength and vital capacity improved and remained improved over one year of follow-up (22). A second patient had failed to respond to treatment with prednisone and azathioprine. Over five weeks, 150 rads were given which resulted in an increase in muscle strength and normal CPK levels by ten days (23). Ten weeks later, a muscle biopsy showed resolution of the myositis. Six months later, however, the patient had relapsed.

Cyclosporine A has been used in a few cases of steroid-resistant polymyositis with mixed results. In one case, for example, a dose of 3 mg/kg of cyclosporine A resulted in a drug level in the therapeutic range of 200–300 ng/dL (24). The patient improved significantly. Recently, however, two polymyositis patients were reported who did not respond to cyclosporine A (25).

Treatment of Extramuscular Complications of Polymyositis

Polymyositis may affect not only muscle but other organ systems as well. Prior to the use of corticosteroids, for example, it was not uncommon to see large depositions of calcium (calcinosis universalis) in many areas of the body, including subcutaneous tissue and muscle. Much less of that is seen now, since high-dose prednisone is being used. In children, however, this can be a particularly disabling and troubling complication and may continue in spite of control of the myositis (26). Various therapeutic modalities have been attempted. Phosphate binders generally cause osteomalacia before they result in any meaningful decrease in calcification. More recently, low-dose coumadin has been suggested because of its effect on bone gamma carboxyglutamic acid (27). Occasionally, surgical excision of particularly large masses of calcium may be necessary.

An arthropathy has been described in polymyositis (28, 29). This may, at times, be destructive, and calcific deposits have been noted in the synovia. Bone scans may show increased uptake in the soft tissues around the joints, especially those in the hands. On occasion, subluxation of the thumb interphalangeal joint requires stabilization.

Interstitial pneumonitis may develop in polymyositis, as it does at times in other connective-tissue diseases (30). It may be quite severe and mask the underlying myositis. It is felt that early treatment with corticosteroids may lessen the interstitial infiltrates and improve lung function (31). Once fibrosis occurs, of course, no therapy is beneficial.

On occasion patients with polymyositis develop dysphagia, which is usually related to weakness of striated muscle in the nasopharynx. In others, crycopharyngeal muscle dysfunction may occasionally require myotomy (32).

Although slight myoglobinuria is not uncommon in polymyositis (33), in a few patients it may be a serious complication. In some of these, dialysis may be necessary.

Summary

The treatment of polymyositis should begin as early as possible and requires high-dose prednisone, generally 60 mg/day, preferably in divided doses until the CPK normalizes. Slow prednisone tapering is then possible if the CPK level remains normal. Reductions of about 10% a month are reasonable. Strength slowly returns, although many patients are still disabled at the end of one year. Later, if the disease is well controlled, cautious switching to every-other-day prednisone may be permitted.

Immunosuppressives have proven to be useful. Azathioprine seems particularly useful when included with prednisone at the beginning of therapy. It does not seem to be as useful a drug as methotrexate in the steroid-resistant patient. Although methotrexate is useful, high dosages are required, generally in the range of 25–50 mg intramuscularly or intravenously each week. Later, when the disease is under better control, slow tapering of the prednisone and the methotrexate may be possible. The role of low-dose oral methotrexate, in the range of 7.5–15 mg per week, as used in rheumatoid arthritis patients, is unclear.

Other immunosuppressives have not been widely used. Cyclophosphamide has been used in too few patients to make any statement concerning its usefulness. Two patients were reported to be improved by addition of chlorambucil plus methotrexate to their prednisone. Cyclosporine A, used primarily in organ transplantation, has been used in various connective-tissue diseases but only in a few patients with polymyositis, with mixed results. Total body irradiation has been reported to be useful in two patients with resistant polymyositis but remains a treatment of last resort.

The Role of Viruses. There is evidence that viruses may play a role in at least some cases of polymyositis. For example, patients with hypogammaglobulinemia may develop a polymyositis-like illness secondary to echovirus infection (34). Influenza has also caused a polymyositis-like myopathy (35) with myoglobinuria. More recently, a few cases of patients with AIDS have developed a myopathy indistinguishable from polymyositis (36), and linear amino acid sequences in certain viruses demonstrate homology with enzymes closely related to those recently identified as autoantigens in polymyositis (37). Future therapeutic research in polymyositis might consider the use of newer antiviral agents.

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Humoral Immunity in Polymyositis And Dermatomyositis

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Humoral autoimmunity to several soluble antigens has highlighted an expanding area of research in the polymyositis syndromes. Although it has been known for a number of years that antinuclear antibodies and rheumatoid factors are present in a proportion of such patients, the new era of this research has focused on defining single antigen-antibody reactions that are proving to be highly disease-specific and, even more exciting, associated with disease subsets. These responses not only have diagnostic specificity, they provide clues to the etiology of these diseases which are explored in this review.

Overview of Myositis-Specific Antigen-Antibody Reactions

The defined specificities (Table 1) were arbitrarily named after either reference patients, disease associations, or simply "precipitin line" (PL). The myositis-associated antibodies include anti-Jo-1 (anti-histidyl-tRNA synthetase) (1, 2), anti-nRNP (anti-U1 small nuclear ribonucleoprotein) (3, 4), anti-PM-Scl (5), anti-Mi-2 (6), anti-Ku (7), anti-PL-7 (anti-threonyl-tRNA synthetase) (8) and anti-PL-12 (anti-alanyl-tRNA synthetase) (9). Additional antibodies have been described in dermatomyositis (DM)/polymyositis (PM) (see below).

Anti-nRNP is associated with myositis, particularly in overlap syndromes, even though it is more commonly found in other conditions, such as systemic lupus erythematosus. Anti-Ro/SSA, anti-La/SSB, anti-Sm, and a few other autoantibodies are primarily associated with other connective-tissue diseases, but may occur in patients with DM/PM, also usually in patients with overlap syndromes, and no independent association with myositis has been shown. A few additional patients have precipitin lines in immunodiffusion (ID) that cannot be identified with a standard reference serum. One or more antibodies can be detected by ID in over half (55%–60%) of adult patients with myositis (5, 10) but less often in children. Autoantibodies can still be demonstrated in many of the ID-negative patients by using routine indirect immunofluorescence (IIF) on Hep-2 cells. Reichlin and Arnett found antibodies in 89% of sera by one or both of these methods (10). Some patients with negative ID and negative Hep-2 ANA may still have anticytoskeletal antibodies (11). Antimitochondrial antibodies have also been reported in myositis (12), using ID with more purified extracts.

Certain properties of the myositis-associated antibodies should be noted. First, there is heterogeneity of antigenic specificity (1, 10), the most common, Jo-1, being present in only 20%. Second, the antibody response is often strong (ANA titers commonly over 1/1000) but usually highly selective, with only one or a few specific proteins targeted by an individual patient. By ID, the myositis-associated antibodies (anti-Jo-1, anti-Mi-2, anti-PM-Scl, anti-Ku, anti-PL-7, and anti-PL-12) do not occur together, but they may coexist with anti-Ro, anti-La, or anti-nRNP (antibodies characteristic of overlap patients). Third, some of the myositis-associated antibodies are disease-specific. This is clearest for anti-Jo-1 and anti-Mi-2, but anti-PM-Scl, anti-PL-7, anti-PL-12, and anti-Ku are most often seen in myositis patients. Finally, the antibodies often have subgroup specificity.

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TABLE
Autoantibodies to Nuclear and Cytoplasmic Antigens in Dermatomyositis (DM)/Polymyositis (PM)

Antibody	% of patients (ref)	Characteristic subgroup
Group A*		
Anti-Jo-1 (histidyl-tRNA synthetase)	18 (10)	PM-ILD
Anti-PM-Scl	8 (10)	PM-Scleroderma
Anti-Mi-2	8 (6)	DM
Anti-Ku	<1	Overlap
Anti-PL-7 (threonyl-tRNA synthetase)	3 (15)	PM-ILD
Anti-PL-12 (alanyl-tRNA synthetase)	3 (9)	PM-ILD
Anti-SRP (signal recognition particle)	uncommon (33)	PM
Anti-Fer, Mas, etc. (other tRNA associated antigens)	rare (28)	PM
Group B		
Anti-nRNP (U1 small nuclear RNP)	13 (10)	Overlap
Anti-Ro/SS-A	7 (10)	Overlap
Ro/SSA + La/SSB	2 (10)	(Sjögren's, SLE)
Anti-mitochondrial	24 (12)	?
Anti-cytoskeletal	86 (11)	all

ILD, interstitial lung disease; SLE, systemic lupus erythematosus.

* Antibodies listed in group A are usually found in serum from patients with myositis or myositis overlap syndromes. Those in group B are more commonly found in other conditions, but also occur in PM/DM. The most characteristic subgroup is described, but many may occur in other groups.

Anti-Mi-2. In 1976, Reichlin and Mattioli (13) described an antibody (Mi) reacting with calf thymus extract by complement fixation, and showed that it occurred in 60% of sera from DM/PM patients but not controls with muscular dystrophy or other connective-tissue diseases (without myositis). Anti-Mi was the first antibody associated with myositis without overlap features. Prototype Mi serum reacted with two different antigens by ID, Mi-1 and Mi-2. Anti-Mi-1 was rarely found in other sera and was not specific for myositis (14).

Anti-Mi-2 was most likely the original Mi antibody, although it was detected in lower frequency (6). We have found anti-Mi-2 only in DM/PM, except for one patient with a rash compatible with DM who had no myositis. It is found in about 8% of DM/PM patients using the ELISA technique. It is almost exclusively found in DM (as opposed to PM), where its frequency approaches 20% (by ELISA) (6). It is the only autoantibody associated only with DM, although others, such as anti-PM-Scl, are sometimes found in DM. It is most frequent in adult DM, but is found in occasional patients with juvenile DM (JDM) and DM with malignancy. The finding of the antibody in at least a few patients in all DM subgroups may be significant in understanding the relationship between different forms of DM.

Mi-2 antigen is a nuclear protein that shows 2 bands on polyacrylamide gels (6), but little else is known of its nature or function.

Anti-Jo-1 and Other Anti-Cytoplasmic Antibodies. Anti-Jo-1 was defined in 1980 by Nishikai and Reichlin (1), and has been found in approximately 20% of patients in a number of studies on genetically different populations (5, 10, 15, 16). Walker et al recently found a higher frequency (44.5% of all myositis patients and 65% of active-disease patients) (17). There is very high myositis specificity for this antibody. We have not found the antibody in any patients without myositis in extensive testing of sera of patients with autoimmune diseases over many years. It is quite uncommon in DM in most studies except that of Walker et al (17), but even in its most common group, adult PM, it is usually found in less than half of patients (30–40%). It is rare in children and has not been reported in myositis with malignancy. Anti-Jo-1 may be seen in patients with overlap syndromes, most commonly with Sjögren's syndrome (10).

There is a strong association of anti-Jo-1 with interstitial lung disease (ILD), now documented in at least 4 patient populations. Yoshida et al (16), in Japan, found ILD by x-ray in all 9 patients with anti-Jo-1, but in only 22% of those without it. Bernstein et al (18) found anti-Jo-1 in 68% of myositis patients with ILD, but in only 7.5% without ILD, among 72 British myositis patients studied. It was also found in 2 of 62 patients with ILD without myositis. Hochberg et al (19) found ILD in 50% of anti-Jo-1 patients (in the U.S.), and recently Walker et al found anti-Jo-1 to be associated with ILD in Australian patients (17).

The clinical course of some of the patients with this syndrome of myositis and ILD may be dominated by the lung disease (20), which may be severe and fatal. Bernstein has suggested that there are other clinical features associated with the Jo-1 antibody (21), including arthritis, sicca syndrome, Raynaud's phenomenon, and sclerodactyly.

Anti-Jo-1 is also linked with HLA-DR antigens. Arnett et al (22) found that 64% of 11 anti-Jo-1 patients had DR3, vs. 22% of 36 anti-Jo-1-negative patients ($p < 0.05$), and all anti-Jo-1 positive patients had either DR3, DR6, or both ($p < 0.01$). This may reflect direct control of antibody production by D-region immune response genes, as suggested for anti-Ro/SSA and anti-La/SSB (23), but whether the association is primarily with anti-Jo-1 or with the associated clinical syndrome has not yet been determined (21).

The Jo-1 antigen is the enzyme histidyl-tRNA synthetase (2), which attaches histidine to its cognate tRNA, activating it for incorporation into nascent polypeptide chains. This was discovered after Hardin et al (24), using immunoprecipitation, found that a specific type of tRNA was contained in the antigen recognized by anti-Jo-1 sera. This tRNA was found by Rosa et al (25) to be the tRNA for histidine (tRNA^{his}). The antigen itself, however, was known to be a protein. Histidyl-tRNA synthetase has a high affinity for tRNA^{his} and may exist as a complex with it. Mathews and Bernstein (2) showed this enzyme to be the antigen by demonstrating inhibition of its activity in vitro. The inhibition was specific for histidine and for anti-Jo-1. The identity of Jo-1 as his-tRNA synthetase was directly confirmed by showing that purified Jo-1 antigen had synthetase enzyme activity (26).

Antibodies to threonyl-tRNA synthetase (anti-PL-7) have been described (8, 27), occurring in 3%–4% of myositis patients (15). Antibodies to alanyl-tRNA synthetase (anti-PL-12) have also been observed (9), in about 3% of myositis patients. Both anti-PL-7 and anti-PL-12 have been seen in rare patients without recognized myositis. Sera with antibodies to thr-tRNA synthetase and his-tRNA synthetase react only with the enzyme itself, while sera with antibodies to ala-tRNA synthetase also have antibodies to tRNA^{ala}, that do not react with other tRNAs (9). The antibodies to the synthetase and to the tRNA can be separated, and Bunn et al (9) postulated that one antibody was the anti-idiotype of the other. Bernstein et al (26) have found anti-PL-7 and anti-PL-12 to be associated with the same clinical subgroup as that of anti-Jo-1 with a high frequency of ILD, Raynaud's phenomenon, and arthritis. The finding of antibodies to a functional class of enzymes associated with a distinctive clinical syndrome is unique among connective-tissue diseases.

Other anticytoplasmic antibodies are found in myositis. A few myositis sera with autoantibodies to other tRNA-associated antigens have been detected. The Fer antibody is directed at tRNA-associated protein(s), and precipitates an array of different tRNAs (28). The Mas antibody is directed at a form of tRNA itself (15, 28). Other sera from myositis patients inhibit translation of preformed mRNA in vitro, indicating that the antigen is involved in protein synthesis (29, 30). Antibody to the small cytoplasmic ribonucleoprotein Ro/SSA, sometimes accompanied by anti-La/SSB, has been found in myositis patients, usually in about 7%–8% (10, 15), although a remarkably high frequency (38%) was found in one study (31). It is usually, but not always, found in patients with overlap of Sjögren's syndrome or lupus. The anticytoskeletal and antimitochondrial antibodies are also anticytoplasmic, but are not specific for myositis. An interesting antibody recently reported in myositis patients (32, 33) is directed at the 54 kDa protein of the signal-recognition particle, a cytoplasmic ribonucleoprotein particle which helps in transport of newly translated secretory proteins across the endoplasmic reticulum. The 68 kDa protein of this particle is believed to be the target of anti-"Alu" antibodies (34) that have been found in a few patients with myositis, although they are also found in other conditions (35).

Thus, there are a number of different cytoplasmic proteins, many of them associated with tRNA or protein synthesis, that become the targets of autoantibodies in myositis. Antibodies to each particular protein are quite uncommon, but there appears to be a predilection for such antibodies not seen in other connective-tissue diseases (8). The other myositis-associated antibodies are not directed at cytoplasmic or tRNA related antigens; Mi-2, Ku and U1nRNP are nuclear antigens, and PM-Scl is nucleolar.

Anti-nRNP. In 1971, Sharp et al (3) described an overlap syndrome of SLE, scleroderma, and PM (mixed connective-tissue disease) associated with antibodies to "extractable nuclear antigen," the first specific autoantibody associated with any form of myositis. The antigen (nRNP) has been identified as the U1 small nuclear ribonucleoprotein particle, which contains the U1 small RNA along with 9 proteins, ranging from 12 to 68 kDa-molecular weight. This particle has been ascribed a role in messenger RNA processing. The antibodies are directed at protein components of the particle, although precipitation and hemagglutination reactions require the RNA to be present. Anti-Sm also reacts with this particle but reacts with different proteins that are also found on other small nuclear RNPs (U2, 4, 5, and 6). Sera from a few patients with PM/scleroderma overlap (36) have both antibodies reacting only with the U2nRNP as well as other antibodies to U1nRNP.

Anti-nRNP can be found in SLE with or without overlap, but is very common in SLE patients with an associated PM-like myositis. There is some evidence that sera with anti-nRNP from patients with overlap syndromes (classified as MCTD), including those with myositis, are more likely to react with the 68 kDa protein than anti-nRNP sera from patients with SLE alone (37). Anti-nRNP is usually found in 10% to 15% of the total DM/PM population (5, 10, 15), many of whom have overlap syndromes, although one British study found an unusually high prevalence in all adult PM/DM subgroups (38). Anti-nRNP may also be associated with myositis with ILD (21, 38). Anti-Sm is rare in myositis, always found in association with anti-nRNP, and only found in patients with overlap with SLE.

One recent report describes an antibody to a 56 kDa protein that is part of a large heterogeneous nuclear ribonucleoprotein particle that is also involved in RNA processing (39). This antibody, which was associated with antibody to another protein of 68 kDa, required Western blotting for detection. It was found to be very common in myositis and SLE-myositis overlap, but not in SLE alone.

Anti-PM-Scl. In 1977, Wolfe et al (40) described an antibody (anti-PM-l) found in 61% of DM/PM patients, including 7/8 patients with myositis-scleroderma overlap. Subsequent studies have shown that more than one antibody was being detected. The unique specificity, labeled PM-Scl, was still associated with myositis/scleroderma overlap (5), but was found in only 12% of 77 such patients in one study (41). A number of other antibodies, including antibodies to U1nRNP, U2nRNP (36), Ku, Ro/SSA, Jo-1 and others, are also found in this syndrome. It may also be seen in patients with DM/PM without overlap, and occasionally in scleroderma without evidence of myositis. In some cases, the myositis is present initially and resolves or responds to treatment while the scleroderma persists (21). Anti-PM-Scl has been associated with ILD (21, 41), which could be a part of the overlapping scleroderma. We have seen a few patients with this antibody without overt myositis or scleroderma.

Although the function of the PM-Scl antigen is unknown, it appears to be a nucleolar protein (42, 43) that may have a preribosomal origin (43) because its expression is inhibited by drugs that suppress rRNA transcription. The fact that this nucleolar myositis antigen is associated with scleroderma overlap is interesting in view of the general association of scleroderma with antinucleolar antibodies (45) (such as anti-RNA polymerase I (46), antifibrillarin (47), and others). Bernstein et al (15) found the antigen to contain three polypeptides of 26-36 kDa, whereas Reimer et al found it to be a particle of 11 polypeptides and no RNA (43), with a 90 kDa antigenic component (44).

Anti-Ku. Anti-Ku, described by Mimori et al in 1982 (7), was originally found in 9 patients from Japan, at least 7 of whom had overlap syndromes involving myositis, particularly with scleroderma. It is less common in U.S. or British myositis patients (as opposed to anti-PM-Scl, which is less common in Japanese patients). We have observed only one patient with anti-Ku (a patient with PM-scleroderma overlap). It also occurs in SLE (48).

The structure of the Ku antigen has been studied in detail (49), but the function is not as clear as it is for Jo-1. Ku is a nonhistone DNA-binding protein with 2 polypeptide chains of 70 and 80 kD, both of which are usually antigenic. It appears to bind to internucleosomal segments of DNA, and can bind in vitro to free ends of double-stranded DNA segments, possibly indicating a role in DNA repair.

IIF Pattern. Most of these specific antibodies can be detected (but not specifically identified) by IIF with cultured human cells (Hep-2 or KB cells). However, up to one-third of sera with anti-Jo-1 will be negative at the screening dilution, and in some others the pattern will be predominantly or exclusively nuclear (10), likely representing other antibodies. Anti-Jo-1 itself gives a cytoplasmic pattern (50). The other antisynthetases also give cytoplasmic staining (8), sometimes in very high titer. Anti-PM-Scl gives a nucleolar ANA pattern, often with associated nuclear staining. Anti-Mi-2 shows a homogeneous nuclear pattern sparing the nucleolus, often in high titer. Anti-Ku gives a fine-speckled nuclear pattern sparing the nucleolus.

Clinical Value. Antibodies to the cytoskeleton are found in sera from myositis patients, but they are commonly found in a large number of conditions, including most other connective-tissue diseases as well as other autoimmune diseases, in patients with recent viral infections, and in normal persons. Senecal et al (11) found antibodies to intermediate filaments, microfilaments, or both, in almost all of their patients with myositis or myositis-scleroderma overlap. Despite the wide distribution of these antibodies, these investigators felt that the antibodies were more closely associated with DM/PM than with any of the other connective-tissue diseases.

This group of antibodies associated with myositis and myositis subgroups can be important to the clinician for their value in diagnosis and classification. These antibodies (except for anticytoskeletal antibodies) are rare in other myopathies and neuropathies and their presence may therefore be useful in differentiating DM/PM from other myopathies. Some of the antibodies, including anti-Jo-1 and anti-Mi-2 in particular, may be useful in differentiating myositis from other connective-tissue diseases. The finding of one of these antibodies suggests that evidence of myositis should be sought. If anti-Jo-1 is found, the patient should be evaluated for the presence of ILD, and caution is indicated in administering therapies with potential lung toxicity (such as methotrexate). Some have found that anti-Jo-1 titers fall when the disease is inactive (16), but others have found no relationship to disease activity (18).

Potential Clues to Etiology. The mechanism for the generation of the antinuclear and anticytoplasmic antibodies is unknown, and is the subject of current research in DM/PM as well as other connective-tissue diseases. The impression that the development of these antibodies is related to the primary inciting event rather than being secondary to muscle damage comes from the disease and subgroup specificity of the antibodies, and the highly selective nature of the response. Although the factors that produce the disease may be directly responsible for the production of the antibodies, production of the antibodies in response to these factors undoubtedly requires a genetically susceptible host. Genes of the HLA-D region are likely to contribute to determining the susceptible host.

There has been much recent interest in the role of viruses as triggering factors in the etiology of many autoimmune diseases. In DM/PM, interest has centered on enteroviruses, a group of small RNA viruses of the picornavirus group. These viruses have muscle tropism, and are capable of inducing acute and chronic inflammatory disease in muscle.

An interesting theory has been suggested for the development of Jo-1 antibodies, based on specific interaction of picornaviruses with Jo-1 antigen. Many plant viruses have tRNA-like structures on their genomes, which can be charged with specific amino acids (51). Picornaviruses share certain similarities of structure with plant viruses, and two are reported to accept amino acids, one of which is Mengovirus, which can accept only histidine (52). This implies a specific interaction with the required enzyme, histidyl-tRNA synthetase.

There may be similar tRNA-like structures on picornaviruses capable of inducing human myositis. This could lead to autoantibodies by formation of a stable complex of enzyme and virus (similar to that of enzyme and tRNA) which becomes antigenic (2). Alternatively, the autoantibodies could develop as an antiidiotypic reaction to antiviral antibodies as a result of complementary viral and antigen structures (53). The finding in different patients of independent, noncrossreacting antibodies to functionally analogous enzymes (different synthetases) and related proteins suggests that the antigens are being targeted because of their function, as in a mechanism resulting from specific viral/antigen interaction. Even if it is not by the proposed interaction, picornaviruses, with an RNA genome that serves as a mRNA, interact directly with the translational apparatus and this may promote the formation of autoantibodies to the proteins involved.

Theoretically, the antibodies may participate in muscle damage either directly, by combining with a specific target on or in the muscle, or indirectly, by leading to the formation of immune complexes. It is unlikely that the antibodies penetrate the cell to react with their recognized antigen, but if a crossreactive specificity were present on the surface of the cell, or if the antigen were expressed on the surface under certain circumstances (as has been demonstrated for anti-Ro/SSA (54)), then the antibodies could play a pathogenic role.

If the antibody or immune complexes played a primary role in muscle damage, deposition of antibody in target tissue would be expected, a finding characteristically seen in lupus. Although this occurs, it is less prominent and less consistent than in lupus, particularly in PM, and not disease specific (55). However, other evidence, such as deposition of the membrane attack complex of complement in muscle vessels in DM (56), does suggest the possibility of antibody-mediated mechanisms in DM. The antibodies may contribute to the vascular disease that is prominent in DM. Further work is needed to determine the potentially pathogenic role of the autoantibodies.

Summary. Autoantibodies to nuclear and cytoplasmic antigens are present in most patients with polymyositis and dermatomyositis. With recent research, a number of antibody specificities have been defined that are associated with these conditions. None is found in all patients, but some are specific for myositis, and closely associated with disease subsets.

Anti-Jo-1 is the most common (20%) and is associated with PM and interstitial lung disease. Anti-Mi-2 is the only antibody that is specific for DM. Anti-PM-Scl and anti-Ku are associated with myositis-scleroderma overlap. Anti-nRNP is associated with myositis/lupus overlap.

These antibodies can be helpful in distinguishing myositis from other myopathies, and certain antibodies may alert the clinician to the presence of interstitial lung disease. They can also give clues concerning the etiology of the disease. The Jo-1 group of antibodies are of particular interest because they are associated with a similar clinical subset, and the antigens are related to each other, with at least three being aminoacyl-tRNA synthetases.

It has been suggested that the antibodies may develop in a genetically susceptible host as a result of a viral infection that is responsible for triggering the myositis. The role of the antibodies in the production of the disease is not known, and no clear relationship of antibody titer to disease activity has been established.

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Cellular Immunity in Polymyositis/Dermatomyositis

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The human PM-like illnesses are a group of disorders characterized by muscle weakness and inflammatory myositis. Clinically recognized subgroups include idiopathic adult polymyositis (PM) and dermatomyositis (DM), PM/DM with connective-tissue disease, DM/PM with malignancy, and juvenile DM/PM (1). Differences in etiologies have been proposed for these subgroups, but the etiology and pathogenesis of each remains uncertain. Current evidence, however, does suggest that infection, immunologic mechanisms, or both, play important roles in the initiation and continuation of these disorders (2, 3). The potential role of humoral immune mechanisms in the pathogenesis of PM is discussed by Targoff and Reichlin in this issue. This review focuses on evidence implicating cellular immunity in PM pathogenesis. Areas reviewed include alterations of lymphocyte numbers and function in patients with PM/DM, the reactivity of lymphocytes from patients with PM/DM to muscle antigens, evidence that immune cells are responsible for muscle damage in patients with PM/DM, and evidence that lymphocytes can alter muscle function (Table 1).

Alterations of Lymphocyte Numbers and Function in PM/DM

There is conflicting information concerning T-cell subsets in patients with PM/DM. Behan et al. characterized the phenotypes of circulating T cells in 18 patients with PM/DM by staining with monoclonal antibodies and analyzing with a fluorescence-activated cell sorter (FACS) (4). Four of five patients with acute PM/DM, 3/8 patients with "chronic active" PM/DM, and 0/5 patients "recovered from PM" had reduced numbers of $CD8^+$ cytotoxic/suppressor cells in the peripheral blood. In an expanded group of patients, including the original data reported, 5/9 patients with acute disease and 4/14 with chronic active PM/DM had reduced numbers of $CD8^+$ cells (5). Based on these findings, these authors suggested that "there is a gross disturbance of immunoregulation" in PM (4). In contrast, Iyer et al. reported normal numbers of circulating T cells and T-cell subsets in 7 patients with PM/DM using monoclonal antibodies and fluorescence microscopy (6).

Abnormal in vitro T-cell function has been described in PM/DM as well. Ransohoff and Dustoor examined autologous mixed lymphocyte reactions (AMLR) of patients with PM/DM (7). These reactions represent proliferation of T cells in response to inactivated, autologous non-T cells. Nine patients with active or inactive PM/DM were compared with age-matched controls. The proliferative response was significantly depressed in the PM/DM patients. The abnormal response was not due to changes in kinetics of the reaction, nor could it be explained by factors such as diminished numbers of stimulator cells.

Suppressed natural killer (NK) cell activity has also been documented in PM/DM patients. NK activity is a spontaneously occurring cytotoxic function, evaluated in vitro by examination of killing of tumor-cell targets by mononuclear cells (MNC). NK cell activity is antibody independent, not HLA restricted, and mediated by a group of lymphocytes which are neither B nor T cells (8). Gonzalez-Amaro et al. examined NK activity in 16 patients with PM/DM, compared with age- and sex-matched controls (9). The mean NK

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activity of patients with PM/DM was lower than that of controls. In patients with "inactive" disease, NK activity was comparable to normals, whereas the cytotoxicity of patients with "active" disease was significantly lower. Unfortunately, no definitions of "active" or "inactive" disease were provided in the report.

Miller et al. measured NK activity as well as antibody-dependent cellular cytotoxicity, another spontaneous cytotoxicity function, in juvenile DM (10). Patients with DM again were found to have diminished NK activity compared with controls. Because only 5 children with DM were studied, no conclusion could be drawn about the impact of disease activity. In contrast to NK activity, antibody-dependent cellular cytotoxic activity was normal.

An important problem with interpreting these findings is that the role of NK function in humans is entirely unknown.

Reactivity of Lymphocytes from PM Patients to Muscle Antigens

Much experimental effort has been devoted to showing that mononuclear cells from patients with PM/DM respond to muscle antigens. Currie et al. reported on the responsivity of mononuclear cells (MNC) to muscle antigens (11). MNC from patients with PM, normal controls, and controls with muscle-wasting disorders were incubated with muscle obtained from normal controls. The mean index of response of PM patients was significantly higher than either control group. However, only 9 of 22 (41%) patients with PM had elevated responses, and 2 of 13 (15%) patients with muscle-wasting disorders, both with muscular dystrophy, had elevated responses.

Esiri et al. reported similar experiments performed to attempt to confirm the earlier findings (12). Twenty-three patients with PM were studied; all but 5 of these were already being treated for their PM. Controls included 17 patients with rheumatoid arthritis, 18 with polymyalgia rheumatica, 9 with osteoarthritis, 16 with muscle-wasting disorders, 9 with unrelated disorders, and 20 healthy controls. Positive controls for the proliferation assays utilized response to the mitogen phytohemagglutinin. Two sources of antigen were used: muscle from a healthy donor and from a patient with myositis. These authors reported mild stimulation of MNC from patients with muscle-wasting disease and mild to moderate stimulation of MNC from patients with PM. Among the patients with PM, patients with untreated disease and active disease despite treatment had higher responses than patients who were symptom free. Four patients were tested before treatment and two subsequent times. In each of these patients, responses dropped within 1–2 weeks after institution of steroid therapy. Three patients were tested with both autologous and allogeneic muscle; responses were comparable to both sources of antigen in these patients. Unfortunately, the responses were not specific for PM. Patients with both muscle-wasting conditions and polymyalgia rheumatica had increased proliferative responses also.

TABLE 1

Experimental Evidence Linking Cellular Immunity to PM/DM

- Alteration of lymphocyte numbers *in vivo*
- Alteration of lymphocyte function *in vitro*
- Reactivity of lymphocytes toward muscle antigens
- Damage of muscle *in vitro* by lymphocytes
- Distribution of mononuclear cells in cellular infiltrates in muscle biopsies
- Inhibition of muscle function by mononuclear cells

Not all such studies have reported positive findings, however. Lisak and Zweiman, using comparable proliferation response assays, found no responsiveness of MNC from 12 patients with PM/DM (13). Whether the lack of responsiveness might be related to corticosteroid or other forms of therapy was not reported.

Using a leukocyte migration assay, Goust et al. demonstrated reactivity of leukocytes from patients with PM to muscle antigens (14). Antigen for these studies was derived from monkeys. Positive responses to this xenogeneic antigen source were found in 12/14 (86%) patients with PM. Again the reactivity was not isolated to patients with PM; 40/46 (87%) patients with myasthenia gravis also had abnormal responses. Human muscle was used as a source of antigen for the patients with myasthenia but unfortunately was not studied in the PM patients.

In an elegant study which has not been repeated, Johnson et al. described the production of the lymphokine lymphotoxin by MNC from patients with PM/DM and its deleterious effect on muscle (15). Eleven patients with PM/DM were studied, including 8 who were untreated. Leukocytes were incubated with autologous muscle and, after dialysis, culture supernatants were assayed for cytotoxicity for muscle. Cultured human fetal muscle was used as a target. Ten of 11 patients with PM (91%) generated cytotoxic supernatants on incubation of MNC with autologous muscle. The one patient without cytotoxicity had inactive disease at the time of study; her disease had been inactive for several months and she was not taking corticosteroids. Cultures of

TABLE 2
In vitro Studies of Cytotoxicity of Mononuclear Cells to Skeletal Muscle in Patients with PM/DM

Author (ref)	Assay muscle source	Method	Cytotoxicity
Currie 1971 (11)	human fetal/ rat fetal	observation	yes
Dawkins 1973 (18)	chick embryo	^{51}Cr release	yes
Haas 1974 (19)	rat embryo	observation, CK	yes
Cambridge 1981 (21)	human fetal	^{3}H-carnitine	yes
Haas 1980 (20)	rat embryo	observation, ^{51}Cr, CK	no
Iannaccone 1982 (22)	human adult/ fetal	amino acid uptake	no

muscle alone from 2 patients were also cytotoxic; the muscle of these patients had marked cellular infiltrates on histologic examination, suggesting that culture of this tissue in fact represented incubation of muscle plus cells. Cultures of cells alone did not generate lymphotoxin. This study showed that MNC from patients with PM are stimulated by autologous muscle to produce a lymphokine which is toxic for muscle.

Each of these studies used crude muscle homogenates as the source of antigen for their various studies. One report described the response of MNC from patients to a specific muscle component. Herrera-Esparza et al. used the leukocyte migration inhibition assay to examine cell-mediated immunity to myoglobin purified from human muscle samples (16). All eight patients with PM/DM studied had significant responses compared with controls with systemic lupus erythematosus or rheumatoid arthritis.

In summary, these studies show that muscle derived from autologous, allogeneic, or xenogeneic sources is recognized as antigenic by lymphocytes from patients with PM/DM.

Evidence that Lymphocytes Are Responsible for Muscle Damage in Patients with PM/DM

Although the studies described above support the concept that MNC from patients with PM/DM are sensitized to muscle, they do not address the question of whether MNC damage muscle in patients with PM/DM. Two lines of evidence support the concept that lymphocytes are directly responsible for muscle damage: examination of in vitro cytotoxicity of muscle targets, and identification of cells in inflammatory infiltrates of muscle from patients with PM.

In Vitro Studies. Studies of in vitro cytotoxicity of MNC from patients to muscle targets are controversial. Some studies have shown destruction of muscle by lymphocytes from patients with PM; other studies have failed to confirm these results (Table 2).

Currie examined the ability of MNC from patients with PM to kill muscle explants from fetal human or rat tissue. His early findings (17) were incorporated into a larger report (11). Cultures were maintained for several days, and cell killing was gauged by microscopic examination of cultures. MNC from 18 patients with PM killed 63/76 (83%) cultures of muscle. Interpretation of this result is difficult because the number of multiple cultures included is not reported, and the distribution of negative results is not described. MNC from patients with PM/DM associated with other connective-tissue disease were more cytotoxic than those from patients with isolated PM/DM. Supporting the fact that cells were responsible for the cytotoxicity, MNC preincubated with antilymphocyte serum lost their ability to kill cultures, and fewer muscle cultures were killed by incubation with serum from PM/DM patients (7/36 cultures, 19%). Among cultures of MNC from 15 control patients with other neurologic disorders, only 8/60 (13%) muscle cultures were killed.

Dawkins et al. used a ^{51}Cr release assay to study in vitro cytotoxicity of muscle by MNC from PM patients (18). Target muscle was derived from chicken embryo muscle cultures. ^{51}Cr-labelled cultures were incubated for 18 hours with MNC or serum plus complement from each of 13 patients with PM/DM. No killing was observed on incubation of cultures with serum plus complement. MNC-mediated cytotoxicity was observed; cells from 4 patients with inactive disease induced no killing, whereas 5/9 patients with active myositis had MNC which killed the muscle cultures. As a control, chicken lung was examined as a target tissue; no killing of these cultures was observed.

A problem with the use of ^{51}Cr labeling of cultured targets is that the label is taken up by all of the cultured cells, and fibroblast contamination of primary muscle cell cultures is frequent. To address this problem, Haas and Arnason used release of creatine kinase (CK) from cultured muscle in addition to visual inspection of cultures as the indices of target-cell killing for cytotoxicity assays (19). For these cultures, rat embryo muscle cultures were utilized. The mean CK release from cultures was significantly greater for 15 patients with PM/DM compared with 15 control patients without muscle disease. Visual damage of cultures was not observed. Among the patients with PM/DM, no difference was noted between patients with active and inactive disease. As had been noted previously, no killing was observed by incubation of cultures with serum alone, although complement was not added to these cultures. Despite these positive findings, in a follow-up paper, Haas was unable to confirm his initial results (20). Again using fetal rat muscle cultures, no killing was demonstrated by visual inspection, CK release, or ^{51}Cr release from labelled cultures following incubation with MNC from patients with PM/DM.

Cambridge and Stern circumvented the problem of fibroblast contamination of muscle cell cultures by labeling the cultures with ^{3}H-labelled carnitine (21). Carnitine is taken up preferentially by muscle, and release of label into culture supernatants would be expected to be due to specific lysis of muscle. Another advantage of this study is that allogeneic rather than xenogeneic muscle was used as the target; muscle was cultured from human fetal tissue. In the 18-hr cytotoxicity assay, muscle killing by MNC from 9 patients with clinically active PM/DM was significantly greater than that mediated by MNC from 7 patients with noninflammatory muscle diseases.

In 1982 Iannaccone et al. published a further negative study (22). Cellular cytotoxicity was sought using separated monocytes or lymphocytes from juvenile patients with inflammatory myositis. Human fetal muscle cultures were incubated with subsets of MNC for 72 hours, washed, and then incubated with ^{14}C-labelled amino acids to assess viability. No cell killing was observed when muscle was incubated with either monocytes or lymphocytes. The authors suggested that in juvenile DM, the target of immunologic reactivity might not be muscle, but rather another tissue such as endothelial cells.

Although the data concerning in vitro cytotoxicity is intriguing, it must be regarded with some skepticism because of the conflicting results and because it is measured with artificial in vitro assays which may have nothing to do with what happens in vivo.

Distribution of Mononuclear Cells in Inflammatory Muscle Infiltrates. Perhaps the strongest evidence for a role for cellular immune mechanisms in the pathogenesis of PM comes from studies which have characterized cells in inflammatory infiltrates of muscle biopsies derived from patients with PM/DM.

A number of authors have reported on the characterization of cells in inflammatory infiltrates. Rowe et al. first reported such findings in 1981 (23). Frozen sections of muscle from 15 patients were stained with monoclonal antibodies recognizing leukocytes, granulocytes, mature T cells, and HLA-DR antigen. Although the frequency of positive findings was not stated, it was noted that significant T-cell staining was present in several of the patients. Importantly, the T cells were found predominantly in sections with more severe inflammation. HLA-DR staining paralleled leukocyte staining, as would be expected. Even in cases in which most of the infiltrating cells were T cells, however, all cells stained with HLA-DR, suggesting that those T cells were "activated."

In a follow-up study, these authors repeated these experiments using muscle from 12 patients with PM and one with DM, staining with monoclonal antibodies directed toward leukocytes, mature T cells, helper/inducer T cells, cytotoxic/suppressor T cells, and HLA Class I and II antigens (24). In 8 patients with untreated PM/DM, most cells stained with the leukocyte and HLA-DR (Class II) reagents, but many cells also stained with T-cell reagents. Again Class II staining in areas containing predominantly T cells was noted, suggesting that the T cells were activated. Of the T cells in untreated patients, most were of the helper/inducer phenotype. In treated patients fewer T cells were found. Another important finding was the observation that Class I HLA antigens were greatly varied in distribution in the biopsies. Muscle-fiber membranes usually did not stain for Class I antigens, but damaged fibers often showed both cytoplasmic and membrane staining.

Adding to this literature, Giornio et al. reported on studies of sections from 12 patients with PM, 8 with DM, and 6 with PM/DM with other connective-tissue disease (25). These authors noted that T cells were the predominant lymphocyte cell type, mostly comprised of $CD4^{+}$ helper/inducer cells. No difference in distribution of cell markers was noted between the patient groups, and no difference was observed by site of the infiltrate, whether perivascular, perimysial, or endomysial. These findings have been corroborated by Lemoine et al. (26).

The most detailed studies of distribution of mononuclear cells within inflammatory infiltrates of muscle biopsies have been reported by Engel and Arahata in a series of papers. In these studies they have carefully analyzed findings from distinct groups of patients with inflammatory myopathies to note important differences in pathologic mechanisms of muscle damage within these groups.

In their first paper they examined biopsies

TABLE 3

Mononuclear Cell Localization in Muscle of Patients with PM/DM

	DM			PM		
	Perivasc	Perimysial	Endomysial	Perivasc	Perimysial	Endomysial
B cells (%)	40	15	11	16	5	1
T cells (%)	36	49	55	56	56	71
Macrophages (%)	24	35	33	27	37	29
B/T ratio	1.5	0.3	0.2	0.2	0.1	0.0

Adapted from Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies: 1. Quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibers invaded by T cells. Ann Neurol 1984; 16:193–208.

from patients with DM, PM, inclusion-body myositis, scleroderma, Duchenne dystrophy, and normal controls (27). In all of the biopsies from patients with inflammatory myopathies they found mixed exudates consisting of T cell, B cells, and macrophages. Natural killer cells were rare in the biopsies. In the patients with DM and PM, T cells were more numerous in endomysial sites than in perivascular areas, whereas B cells were more numerous in perivascular locations (Table 3). At all sites, B cells were more frequent in DM patients than in PM patients, and T cells were more frequent at all sites for the PM patients. Of T cells, a positive gradient for CD8$^+$ suppressor/cytotoxic cells was observed, progressing from perivascular to endomyosial locations, while there was a negative gradient for CD4$^+$ helper/inducer T cells (Table 4). More activated, Ia (HLA-DR)-bearing T cells were found at endomysial sites. The authors interpreted these data as showing that different cell types are more important in different inflammatory myopathies. Additionally, they concluded that T-cell-mediated muscle fiber injury likely occurred in PM and that a local humoral immune response might be more important in DM.

A companion paper examined necrosis of muscle fibers in PM patients in greater depth (28). Biopsies from 6 patients with PM were stained with acid phosphatase to identify live and necrotic muscle fibers and stained with monoclonal antibodies to identify T-cell subsets and Ia markers. This quantitative approach permitted assessment of cells invading and damaging viable muscle fibers compared with cells surrounding and phagocytosing necrotic fibers. Live muscle fibers were attacked primarily by CD8$^+$ cells, whereas 80% of the cells invading necrotic fibers were macrophages. Many of the invading CD8$^+$ cells were Ia$^+$, activated cells. These observations suggest strongly that in PM, autoreactive T cells invade and injure viable muscle fibers.

In a subsequent paper describing immunoelectron microscopy of biopsies from patients with PM, Arahata and Engel described the sequence of events occurring in the course of muscle fiber invasion by macrophages and CD8$^+$ cells (29). Their photomicrographs beautifully document the invasion of individual muscle fibers by these cells and the ultimate death of the fibers.

A problem with interpretation of these findings has been that cytotoxicity by CD8$^+$ cells is dependent on class I HLA recognition, and normal human muscle expresses class I antigens only weakly (30). This paradox has been explained by the demonstration of much stronger expression of class I antigens on muscle fibers of patients with PM compared with normal controls. As discussed above, Rowe et al. described the increased expression of class I antigens on necrotic fibers as compared with normal-appearing muscle fibers (24). Appleyard et al. also docu-

TABLE 4

Localization of T Cell Subsets in Muscle of Patients with PM/DM

	DM			PM		
	Perivasc	Perimysial	Endomysial	Perivasc	Perimysial	Endomysial
T8/T (%)	42	51	68	46	52	82
T4/T (%)	61	52	34	56	51	18
T4/T8 ratio	1.7	1.1	0.5	1.2	1.1	0.2
Ia$^+$/T (%)	17	6	22	21	15	37

Adapted from Arahata K, Engel AG, Monoclonal antibody analysis of mononuclear cells in myopathies: 1. Quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibers invaded by T cells. Ann Neurol 1984; 16:193–208.

mented class I antigen expression on muscle fibers of patients with inflammatory myositis and patients with some but not all muscular dystrophies (31). It has been postulated that increased expression of class I antigens renders them susceptible to killing by CD8$^+$ T cells. How the increased expression of class I antigens might come about has been investigated by Isenberg et al. (32). Again staining biopsy sections from patients with PM with monoclonal antibodies, these investigators demonstrated that areas of muscle from PM patients expressing class I antigens were closely matched with areas containing α, β, and γ interferon, and infiltrates of T cells. Thus, interferon release, arising either from local tissues following viral infection, or from activated T cells, might induce class I antigen expression on muscle, rendering it susceptible to destruction by activated cytotoxic T cells.

Evidence that Lymphocytes Might Alter Muscle Function in PM/DM

In addition to considering that cellular immune mechanisms are responsible for direct damage of muscle, there is evidence that immune cells may alter muscle function. This is an appealing concept because muscle weakness is frequently out of proportion to muscle fiber loss. Additionally, the concept might explain why some patients have a rapid response to corticosteroid therapy.

In two studies, Kalouvidouris et al. have described alterations of muscle function induced by mononuclear cells. In an initial study, MNC from normal donors were cultured with the mitogens phytohemagglutinin-P and concanavalin A (33). When supernatants from these cultures were incubated with sarcoplasmic reticulum membranes from rats, suppression of ATP-dependent calcium accumulation was demonstrated. Because calcium release from sarcoplasmic reticulum is an important step in muscle contraction, suppression of calcium release could contribute to weakness. In a subsequent paper Kalouvidouris and Meiss described suppression of contractility of mouse muscle strips in a culture bath (34). Again, supernatants of MNC from normal individuals incubated with mitogens were examined and found to suppress contractility of the muscle strips. Although the MNC tested were not from patients with PM/DM but from normal donors, these experiments demonstrated that MNC are able to release a humoral substance(s) that interferes with muscle contraction, possibly by interference with calcium release from sarcoplasmic reticulum.

Summary

Several lines of evidence suggest that cellular immune mechanisms play an important role in the pathogenesis of human PM/DM. These range from demonstrations of simple differences of numbers of T cells in vivo in patients with PM/DM, to alterations of in vitro tests of immune function. Although controversial, some evidence suggests that immune cells from patients with PM/DM can kill muscle in vitro.

Probably the best evidence to support a role for cellular immunity in disease pathogenesis stems from examination of the cells present in inflammatory infiltrates of muscle from patients with PM/DM. In these studies, careful analysis has shown that cellular immune mechanisms, mediated by CD8$^+$ cytotoxic cells, are responsible directly for muscle fiber damage in patients with PM. In contrast, CD4$^+$ helper cells are found in muscle of patients with DM, but humoral mechanisms may be more directly involved in muscle damage in these patients.

Although many details remain to be understood, the combination of these findings argue strongly that cellular immune mechanisms play an important role in the pathogenesis of PM/DM.

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Animal Models of Myositis

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Patients with idiopathic inflammatory muscle disease, superficially the most homogeneous clinical group of rheumatic disease patients, almost surely have a group of diseases with various etiologies and pathogenetic mechanisms. With respect to etiology, acute myositis in humans can certainly be caused by a number of viruses and by drugs, and several pieces of evidence suggest that viruses may cause some cases of polymyositis or dermatomyositis. With respect to pathogenesis, chronic inflammation with cells from the immune system is incontestably present, and autoantibodies are often present too, so the disease falls easily into the category of autoimmune diseases. As knowledge of the immune system has deepened, however, the inadequacy of that categorization has become clearer.

In a disease with even this limited diversity, no single example of an animal analogue can be expected to mimic fully the human disease. Thus the animal models studied so far shed less light on the spontaneous human disease than they illustrate how diverse, complicated, and still obscure are the pathogenetic mechanisms at work.

Spontaneous Animal Myositis

A spontaneous dermatomyositis in collies and shetland sheep dogs which differs substantially from the adult human disease has been beautifully described and reviewed recently by Hargis and Prieur (1). The centrifugal rash is said to resemble childhood dermatomyositis, but muscle distribution and pathology differ substantially.

A mouse-like rodent, Mastomys, has been noted to develop thymomas. Among those animals with this tumor, about a fifth have an associated myositis (2).

Mice, like humans, develop myositis following infections with *Toxoplasma* (3). The illness in mice following *Trypanasoma cruzi* infection is a chronic polymyositis from which the organism can be recovered only infrequently. Splenic cells enriched for T cells from infected mice, when cultured in vitro with the organism, developed cytotoxicity to uninfected myoblasts. A lymphokine may have been responsible for the cytotoxicity.

The simian acquired immunodeficiency virus, a retrovirus resembling HIV, caused polymositis in about half of rhesus monkeys inoculated with tissue extracts from affected animals or with tissue-culture-grown virus (4). The pathology resembled the human disease, and virus could be isolated from the muscles. The disease did not appear to be due to opportunistic organisms.

Muscle-Extract-Induced Myositis

The success of the model for experimental allergic encephalitis caused by the injection of brain extracts and the popularity of the then single concept of autoimmunity led, beginning over thirty years ago, to extensive study of myositis induced by injecting muscle extracts into various species. The disease was mild and difficult to induce, and the antigen(s) responsible for it were not, in contrast to myelin basic protein, well-defined. These limitations of this model, well-discussed in excellent reviews by Whitaker (5) and by Dawkins (6), led to its being virtually abandoned over a decade ago.

Recently, it has been revived by Rosenberg, Ringel, and Kotzin (7). They chose to use mice which had not been used successfully before. They prepared saline extracts of *syngeneic*

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muscle from nine inbred strains of mice and injected an emulsion of the extract with complete Freund's adjuvant subcutaneously two to four times over three weeks. None of the animals developed observable weakness, adjuvant-induced arthritis, or histologic abnormalities in organs other than muscle. Of the mouse strains tested, only the SJL/J developed histologic abnormalities of skeletal muscle. The abnormalities, noted at the time of first examination a week after the last injection and present as late as 11 weeks later, were mild: isolated, scattered muscle fibers, sometimes in small groups, were necrotic and surrounded by a mononuclear cell infiltrate. Sometimes involved fibers without infiltrates or infiltrates without a nearby necrotic fiber were seen. Other fibers showed internalization of nuclei. Two other strains bearing the same H-2 haplotype (H2b) did not develop abnormalities.

Immunoglobulin deposits in muscle, the presence of antibodies to a saline muscle extract by ELISA, and the presence of antibodies to muscle sections by fluorescence staining did not correlate with histologic evidence of necrosis. Although SJL/J mice were positive by these tests, so were some mice without histologic myositis. Furthermore, some SJL/J mice injected with adjuvant alone developed very mild histologic myositis, too.

Virus-Induced Myositis

Following up an early observation of myositis in newborn mice infected with coxsackievirus B1 and reports of isolation of coxsackieviruses from several human cases of myositis, Ray, Minnick, and Johnson deliberately infected newborn mice of several strains with several isolates of coxsackievirus B1 (8). Using a tissue-culture-adapted virus injected intraperitoneally as culture supernatant into one-day-old mice, they found that C3H mice were wholly resistant, but that two outbred strains (Swiss and COH) and inbred Balb/c mice became ill and suffered considerable mortality.

Although the affected strains had, to a variable degree, myocarditis, hepatitis, interstitial pancreatitis, and encephalitis, among the two random bred strains, up to half the surviving animals developed a progressive clinical weakness of their hind legs which led to a flexion deformity. The hind thighs, extensors, and, to a lesser extent, the gastrocnemius and soleus muscles, became atropic. Histologically, the course was early widespread necrosis, phagocytosis, and later mononuclear infiltration. There was also perivascular cuffing with mononuclear cells. Later, sarcolemmal nuclear proliferation, regeneration, and fatty infiltration developed, and inflammation subsided. Dystrophic calcification was found in a few animals. A curious feature was that the right side was more affected than the left. No changes in the central or peripheral nervous systems were found.

Several fresh isolates of coxsackievirus B1 from human sources were tested. Three caused myositis in newborn mice, and three did not. Thus, in the model, the importance of the host and of the viral strain were established.

This model has been more extensively studied by Strongwater, Dorovini-Zis, Ball, and Schnitzer (9) and by Ytterberg, Mahowald, and Messner (10). Using the same virus strain, designated coxsackievirus B1 (Tuscon) and Swiss mice injected within two days of birth, Strongwater et al. again found the onset, within a few days, of muscle cell necrosis and phagocytosis followed by acute and then chronic inflammation, muscle cell regeneration and dystrophic calcification and fatty infiltration. Active myocyte regeneration was still evident more than two months after infection. Again, hind limbs were most affected, and sometimes one side was more affected, leading to a waddling gait. Throughout the course of their illness, the mice showed abnormal electromyograms, with fibrillations, positive sharp waves, and complex repetitive discharges.

Although the inflammatory and healing processes were long-lasting, virus could be cultured from muscle for less than two weeks, and viral antigen could be detected by indirect immunofluorescence within muscle cell cytoplasm for the same period. An immune response developed within the first week after infection, and neutralizing antibodies remained present in high titer thereafter. Together, these findings suggest that although a direct viral myositis initiated the illness, another mechanism sustained it.

Ytterberg and his colleagues, by using the same virus strain and Swiss mice which were either homozygous (T-cell deficient) or heterozygous (normal T-cell function) for the nude gene, explored the role of T cells in the pathogenesis of the myositis. Homozygous nude and heterozygous mice both developed acute myonecrosis and weakness within a few days, accompanied by edema and acute inflammation. Both cleared culturable virus early in the second week (between days 7 and 11), and both mounted identical antibody titers by ELISA measured four weeks after infection. Furthermore, LD^{50} of the virus was the same for both.

The homozygous nude mice, despite their profound immunodeficiency, recovered fully. Their muscles appeared almost normal several weeks after infection. By contrast, weakness, present in 80% of the surviving heterozygotes, persisted unabated throughout the period of observation. Histologically, the affected muscles showed continuing disease four weeks after infection; degeneration, regeneration, and inflammation remained. The nature of the inflammatory cells is not described. It was possible to cause chronic myositis in infected homozygous nude mice by transferring spleen cells from heterozygous mice two days after infection. The spleen cells of uninfected donors were as effective as those from infected donors.

Together, these observations support the view that a self-sustaining myositis, occurring after clearance of the virus and in the presence of a normal humoral immune response, requires normal T-cell function. Further exploration of this model will be most interesting.

Our laboratory has studied a myositis which can be induced in adult mice by infection with a myotropic variant of encephalomyocarditis (EMC) virus (11). EMC virus, like coxsackievirus B1, is a picornavirus, but belongs to the cardiovirus rather than the enterovirus subgroup. The variant we use (EMC-221A) was selected in vitro on mouse embryo cells and later in vivo by heart passage, and was found to produce myositis in adult SJL/J mice. Another plaque-purified variant (EMC-D) from the same selection produced diabetes, but only negligible myositis or myocarditis, in several mouse strains. We chose to work with EMC-221A because a related virus was among those which mimic tRNA in an ability to accept an amino acid from an aminoacyl-tRNA synthetase (12). It is enzymes of this family to which several autoantibodies unique to patients with the human diseases polymyositis and dermatomyositis are directed (13).

The EMC-221A variant induced long-lasting myositis and myocarditis in some but not all strains of mice. The disease is clinically evident by the waddling gait, and the cardiac disease is sometimes fatal soon after infection. The myositis is histologically indistinguishable from the human disease. Besides myocyte degeneration and regeneration, there is mononuclear cell infiltration, late perifasicular atrophy, and dystrophic calcification. The serum levels of muscle-associated enzymes, for example aldolase, show an early rise, a return toward normal, and a later secondary rise.

Of the three autoimmune strains inoculated, two were severely affected early (BXSB males and MRL 1pr/1pr females) and one (NZB × NZW F1 females) was not. None of the mice developed autoantibodies to the Jo-1 antigen (histidyl-tRNA synthetase) nor to other ribonucleoproteins, as tested by immunoprecipitation. Thus, the chronic illness does not depend upon the synthesis of these autoantibodies. Conversely, immunization of mice with the Jo-1 antigen does not cause myositis (T. Biswas, L. Love, unpublished observations).

Further studies on viral persistence, viral immunity, and other aspects of the illness are continuing. A myotropic variant of a closely related virus, Mengovirus, produced a similar illness in adult mice (F. W. Miller and L. Love, unpublished observations).

Other Relevant Virus Models

The diseases caused in mice by two picornaviruses closely related to coxsackievirus B1 and to EMC virus have been studied in great detail and shed light on the kinds of disease mechanisms probably at play in the myositis models.

Coxsackievirus B3 has long been known to cause myocarditis in humans and in mice. Woodruff and Woodruff, using the Nancy strain (CB3-Nancy), showed that the acute myocarditis was much diminished in animals which had been thymectomized, irradiated, and bone-marrow-reconstituted, and that infused thymocytes restored the severity of the disease (14). The thymus-deprived mice eliminated virus and raised neutralizing antibodies as well as normal hosts. Gauntt and his colleagues showed that there were strain and sex differences in susceptibility to the acute illness (15).

The acute myocarditis has been explored in great detail by Huber and her colleagues at the University of Vermont. Confirming the role of T cells in the illness, they showed that in Balb/c mice, two types of lymphocytes develop rapidly after infection: a type which binds to and can lyse virus-infected cells, and a type which binds to and can lyse *un*infected myocytes (16). The virus-specific cells are L3T4+, whereas the apparently autoreactive cells are Lyt2+. It is the autoreactive cells which are best able to transfer the disease when injected into infected, thymus-deprived animals (17, 18). Cyclosporine A does *not* block the myocarditis, nor does it affect generation of the autoimmune cells, although it blocks generation of virus-specific lymphocytes (19). Another mouse strain of the same ($H2^d$) histocompatability type, however, develops a similar illness in which (a) IgG antibodies directed against myocytes are found, (b) cobra venom, to decomplement the animal, abrogates the disease, and (c) virus-specific but *not* myocyte-specific lymphocytes develop (20).

Studying a myocarditic coxsackievirus B3, a group at Johns Hopkins has found chronic myocarditis when the virus is given to the suckling mice of some but not all strains (21). They have apparently found a susceptibility locus on chromosome 14 (22). In this illness, susceptible strains of mice develop IgG antibodies specific for cardiac myosin, although titer did not correlate closely with tissue damage (23). Supporting a role for this autoantibody in the development of the disease, however, is the observation that a coxsackievirus B3-susceptible mouse strain developed myocarditis and autoantibodies to cardiac myosin when injected with cardiac myosin, whereas two virus-resistant strains did not (24). In nude mice, viral genome may persist in the heart as late as 56 days after infection, as shown by in situ hybridization (25).

Studies with another picornavirus-induced inflammatory illness illuminate another mechanism of chronic inflammation (26). The chronic demyelinating disease caused by a cardiovirus closely related to EMC virus and Mengovirus—Theiler's virus—has been studied as a model of multiple sclerosis. Susceptibility to the chronic demyelinative illness which develops after intracerebral inoculation of young mice maps to one end of the H2 region (H2D) of the mouse (27). In this illness, late persistence of viral antigens in the nervous system has been described (28), and affected strains develop virus-specific delayed-type hypersensitivity (29). Neither acute virus proliferation nor antibody responses correlate with susceptibility to the late disease, but only susceptible strains develop Ia antigens on the surface of glial or CNS endothelial cells following viral inoculation into the brain (30). The exact anatomic relationship among persistent virus, Ia antigens, and lymphocytic infiltrates is not yet clear.

In summary, in these infection-initiated inflammatory illnesses, a variety of mechanisms has been demonstrated. The use of more sensitive techniques to detect viral persistence and to study the specificity of the lymphoid cells directly infiltrating the lesions, and surely other techniques, are likely to clarify the details of these illnesses. It seems likely, however, that no single mechanism will emerge to explain either these illnesses nor the human illnesses of which they are models.

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